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PSORIASIS

BY

PETER FLESCH (*Conference Chairman*), J. BLEIBERG, A. J. BOLLET, O. BRAUN-FALCO, S. G. CLYMAN, E. C. J. ESODA, G. W. HAMBRICK, JR., E. B. HELWIG, A. L. LORINCZ, D. A. ROE, S. ROTHBERG, M. H. SAMITZ, AND R. E. TURNER

Consulting Editor
PETER FLESCH

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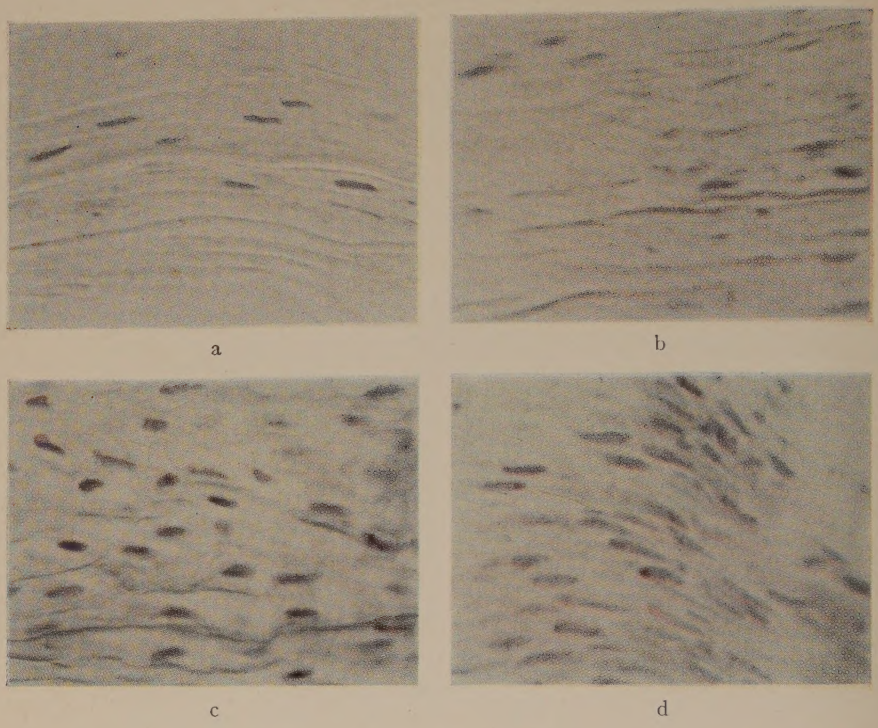

FIGURE 7. (a) Psoriatic scale stained with buffered thionin (×640); (b) psoriatic scale extracted with borate buffer and stained with buffered thionin (×640); (c) psoriatic scale incubated with testicular hyaluronidase and stained with buffered thionin (×640); (d) psoriatic scale incubated with boiled testicular hyaluronidase and stained with buffered thionin (×640). See D. A. ROE, "Application of Paper Electrophoresis to the Diagnosis of Psoriasis: a Study of Psoriatic Scale Extracts," page 983.

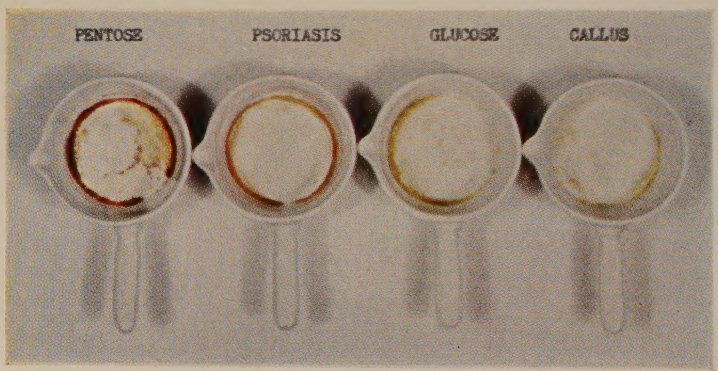

FIGURE 7. Aniline phthalate spot test in aqueous extracts of callus and psoriatic scales. Callus gives an olive-green color reminiscent of hexose, and psoriatic scales give the red color of pentoses. See P. FLESCH and E. C. J. ESODA, "Chemical Changes in Psoriatic Scales," page 995.

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PSORIASIS*

CONTENTS

* This monograph is the result of a conference on *Psoriasis* held by The New York Academy of Sciences on May 9, 1958.

CLINICAL FEATURES OF PSORIASIS

By George W. Hambrick, Jr.
Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

In 1958 psoriasis remains the "great dermatological mystery."[14] As might be expected, its clinical morphology continues to rest on a solid foundation, characterizing the disease as an entity. My purpose is to review the morphologic features of psoriasis.

Historical

Celsus (about 25 B.C. to 45 A.D.) gave us the first recognizable description of psoriasis. The term lepra in the Old Testament included not only psoriasis but various other diseases such as vitiligo, ichthyosis, and elephantiasis.[4] Galen (133 to 200 A.D.) introduced the word psoriasis to describe scaliness of the eyelids and corners of the eyes, and a rough and scaly state of the scrotum, an eruption that was probably not psoriasis.[4] The first classic description of psoriasis comes from Robert Willan[16] in 1801, who continued using the word lepra to denote psoriasis. However, he also first used the term psoriasis in its present connotation for certain features of the disease. It was not until forty years later that Hebra eliminated the word lepra as a synonym for psoriasis.[4] Alibert in 1822 noted the association of joint pains with psoriasis.[19] In 1878 Koebner[4] described his studies of the role of trauma in producing lesions.

Willan's description of psoriasis. An accurate description of psoriasis is contained in the second part of Willan's text,[16] first printed in 1801, which deals with scaly disorders of the skin. "The cuticle is not, however, the only seat of these complaints. They often originate from indurated papulae or larger elevations of the true skin, which by pressure or distention injure the texture of the cuticle, and produce thickened, irregular layers of it. The lepra vulgaris at first exhibits small distinct elevations of the cuticle which are reddish and shining, but never contain fluid. Within 24 hours, however, thin white scales form on their tops. After 3 or 4 days, the small elevations are flattened and at the same time dilated by an extension of their bases to the size of a silver penny. These patches continue to enlarge gradually until they become nearly the size of a crown piece. They always retain a circular or oval form, are covered with dry scales, and surrounded by a red border." According to Willan, the process seldom terminates spontaneously. It continues for several years or during an entire lifetime. The steps leading to its termination are as follows:[16] "First, the incrustation separates from about the centres of the patches, and is no longer reproduced. The scales being farther and farther removed, a circle of red shining cuticle deeply indented appears within the original patch which still retains a broad, hard, scaly ring or border. This border continues 'till the cuticle within it assumes the usual color and texture. It then gradually softens, and the cuticular

lines being extended over it, every vestige of the disease is erased." Other features pointed out by Willan were:

(1) There is a tendency for the lesions to occur over bony sites, such as the elbows and knees.

(2) There is a striking symmetry in the eruption.

(3) Although new lesions continue to appear, the original sites remain unchanged. When a remission begins, all the patches assume a favorable appearance at the same time; those nearest the extremities disappear later than the rest.

(4) The lesions of the scalp extend onto the forehead and temples, forming a crown. The rash is rarely observed on the cheeks, nose, or eyebrows.

(5) Willan noted also that, although one might expect obstruction of perspiration, with disagreeable consequences, in his experience this was not the case.

Incidence

The exact rate of occurrence of psoriasis in the total population is not known; one estimate rates it as high as 1.4 per cent.[8] Among 20,000 men undergoing army induction physicals, 55 (0.27 per cent) suffered from psoriasis.[6] The malady accounts for approximately 6 per cent of all new cases of skin disease seen in hospitals and clinics.[12] It occurs throughout the world, but is generally less common and less severe in tropical areas. All races may be involved, but it is not common in Negroes.

A familial incidence as high as 42 per cent has been reported, with an average of approximately 26 per cent.[10, 13] Whether this fact indicates the hereditary nature of the disease has not been settled. Congenital cases do not occur, although a few have been reported in infancy. Those opposed to the hereditary theory quote the familial incidence in support of other theories of causation. Conjugal cases are quite rare.

Opinions differ as to the role of the emotional make-up in the psoriatic individual; Becker and Obermayer[5] believe neurocirculatory instability is a part of the psoriatic diathesis or state. Along these same lines there is no uniform agreement about the body type that predisposes to psoriasis.[2] The nutritional status of the psoriatic individual has no fixed pattern.

Clinical Picture

Psoriasis may be defined as a chronic, recurrent, inflammatory disease of the skin; it is characterized by circumscribed, erythematous, scaly patches or plaques of varying sizes covered by silvery-white, imbricated scales. The initial lesions are guttate erythematous macules or maculopapules with dry, silvery scale apparent at the beginning. The scale is attached more securely in the center than at the periphery; upon its removal, tiny bleeding points appear (Auspitz's sign). Upon gentle curetting, the scale becomes powdery. Although the initial lesions may persist in guttate form, commonly the lesions increase in size by peripheral extension until they reach a diameter of several inches. They may remain solitary or become confluent with other lesions to form large plaques. The outline of such a lesion is always oval, circinate,

gyrate, or serpiginous, with the convex borders projecting into the normal adjoining skin. As the lesion becomes older, central involution often occurs, even though the active peripheral border is still extending. Ultimately, normal-appearing skin may be present in the centers of such plaques. On the other hand, large plaques without central involution do occur and persist

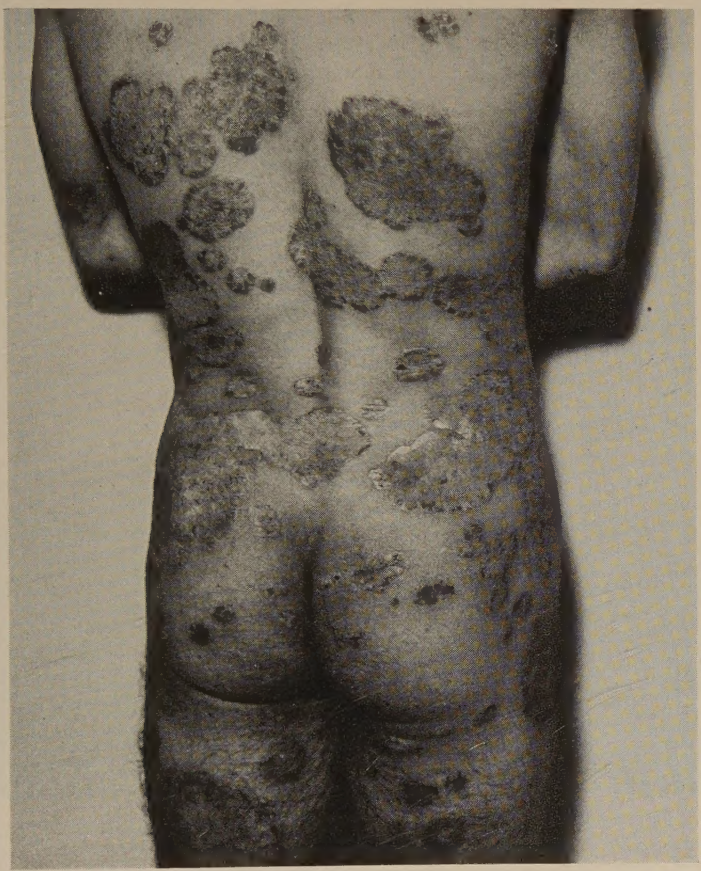

FIGURE 1. Generalized involvement with large plaques of psoriasis occurring in a young adult. Peripheral activity and beginning central clearing are apparent.

for years in this form. Around the individual psoriatic lesion a pale area of normal-appearing skin, 0.2 to 0.5 cm. in width, often is present, especially in treated lesions. This so-called "immunity zone" is not specific for psoriasis, and its genesis is poorly understood. Scarring is not a usual aftermath, although in areas of long-standing edema or in repeatedly traumatized areas, such as the leg, scars may appear. Hyperpigmentation (or, rarely, hypopigmentation) may be a sequel at sites of lesions healed with or without therapy (FIGURES 1 and 2).

There are several other distinctive phenomena related to psoriasis. The Koebner phenomenon, or isomorphic reaction, is the appearance of typical lesions of psoriasis following all types of injury to normal-appearing skin. This accounts for the appearance of lesions at sites of scars or operations. In acute eruptive psoriasis, new lesions may be produced by scratching the skin. The elicitation of this response is related to the acuteness of the psoriasis; it is not produced in recently healed psoriatic sites. Lesions of psoriasis may appear at sites of former drug-eruption lesions, especially in those due to sulfonamides. The Koebner phenomenon is not diagnostic

FIGURE 2. Psoriatic patches on the elbows. The typical silvery-white scale is apparent.

but only suggestive evidence for psoriasis, as it occurs also in other skin conditions.

A second feature of the psoriatic lesion is sweat retention.[15] This interference extends to the central healed area of a lesion and to the surrounding normal-appearing skin (immunity zone). After clearing of the lesion it persists for varying periods. In the usual case this interference with delivery of sweat is not sufficiently extensive to cause any serious difficulties. However, in cases of exfoliative psoriasis with tota' body involvement, sweat retention may be of great importance.

A number of variations in typical morphology are possible. These are pustular, eczematous, seborrheic, or rupioid lesions. These morphologic

variations may be present from the onset or they may develop subsequently; factors such as the site of involvement or external applications play a role. Pustular psoriasis is infrequent; the diagnosis has been used with two connotations: (1) true pustular psoriasis and (2) the pustular psoriasis of palms and soles described by Barber.[3] In true pustular psoriasis the morphology of the lesion is that of psoriasis with the addition of pustules in the plaques. The distribution conforms to that of the usual type of psoriasis, with a prominence of lesions on the palms and soles. Occasionally the initial attack may be characterized by showers of pustules or purulent vesicles. Later these are replaced by psoriatic lesions with or without pustules. Arthritis may appear more frequently in association with pustular psoriasis. In 133 cases of pustular eruption of the extremities, Ingram[11] found that 35 of these had undoubted psoriasis elsewhere on the body. The remaining 98 had no accompanying lesions distinctive for psoriasis. These latter patients fall into the second group described by Barber and Ingram as pustular psoriasis of the extremities. It is probable that this second type of pustular psoriasis is neither clinically nor histologically a variant of true psoriasis; it has features similar to, but not identical with, those of the pustular bacterid of Andrews.[1] In the seborrheic type of psoriasis the lesions are covered with greasy rather than white-silvery scales distributed over the scalp and the flexural surfaces, and this type is often confused clinically with seborrheic dermatitis (in intertriginous areas scales of any type may be entirely absent and only the erythematous base be present). Some investigators believe that within a given lesion there is a mixture of the two disturbances. Initial psoriatic lesions may be eczematous, that is, they may be erythematous patches, not well circumscribed, with fissuring and without silvery scales attached. Eczematization also may be secondary to therapy applied to a previously typical lesion. Eczematous lesions may be quite pruritic, and changes of localized neurodermatitis may be superimposed upon the original process. In a rupioid psoriasis lesion the scales pyramid upon each other, and the thickened, layered, oyster shell-like scales remain attached to their base.

The classic distribution of the lesions in psoriasis is extensor, predominantly on the elbows and knees; however, lesions may be found in a primarily flexural distribution, so-called "inverse psoriasis." Often a mixture of extensor and flexural distribution occurs. Symmetry of lesions is the rule. The trunk and scalp are involved to various degrees. The intergluteal cleft is a common site. In inveterate psoriasis, lesions over the lumbosacral area are quite characteristic. Anteriorly along the hairline a corona of involvement may be present, but large solitary lesions or diffuse scalp involvement are more common. Hair loss does not occur as a result of psoriasis. The auricular folds and the external ear canal may be involved. Lesions restricted to the face are quite uncommon, but are not rare when there is involvement elsewhere. Occasionally lesions of the eyelid and conjunctivitis are encountered. Mucous membranes have been involved rarely. The dorsal surfaces of the fingers may be affected at the interphalangeal joint sites. Typical plaques may occur on the palms and soles; a greater

incidence of pustules within these plaques is noted. The nails show two types of changes: (1) simple stippling or punctate pitting, as if a pinpoint had been pressed into the nail; and (2) a yellow, opaque discoloration with disfigurement and terminal crumbling of the nails secondary to the hyperkeratotic process (FIGURE 3). Involvement of the periungual tissues may be striking or absent. Alterations of the nails may be the only manifestation of psoriasis. Genital involvement consists of typical lesions in the skin of the scrotum and penis, or the labia, frequently associated with prepubic and crural lesions.

The onset of psoriasis is usually gradual, the earliest lesions appearing on the extensor surfaces of the extremities, on the scalp, or both. The number

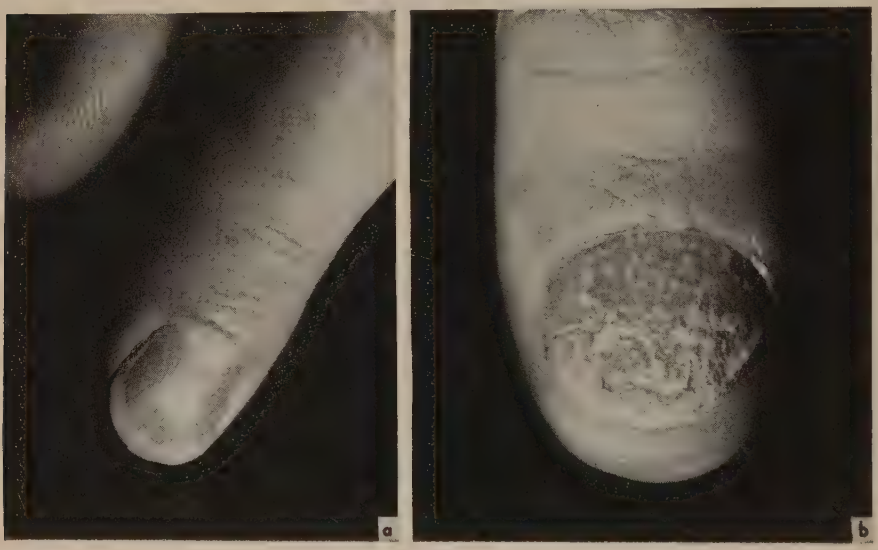

FIGURE 3. Nail involvement in psoriatics. (a) Multiple punctate pits throughout the nail reflect minimal involvement. (b) A more advanced stage, resulting in thickening and keratotic crumbling.

of lesions increases gradually. On the other hand, the onset of the initial or recurrent eruption in some individuals may be abrupt, with the sudden appearance of many lesions often not morphologically typical. The eruption may start without any precipitating circumstance or may be preceded by illness, an accident, or emotional difficulty. The extent of pruritus in psoriatics is unpredictable; however, in acute psoriasis pruritus may be the presenting symptom. The average age of patients with an initial attack is 20 years, although children and, rarely, infants also may be affected.[12] The appearance of a psoriasiform lesion in the aged is infrequent without previous history of such lesions and warrants a careful search for cutaneous lymphoma.

The course of psoriasis is quite variable.[12, 17] Persistence of lesions, partial remission with or without subsequent exacerbation, and complete

disappearance of lesions with or without recurrence are the possibilities. Approximately one sixth of patients have a complete remission, lasting from 1 month to 20 years.[12] However, it is certain that one of the reliable features of psoriasis is its tendency to recur. In the majority of patients, partial clearing of the eruption occurs in the summer (although approximately 14 per cent of patients[12] relate worsening during the summer or after sunlight exposure). Occasionally a patient may have only one attack of psoriasis with clearing and no further involvement throughout his life. Nevertheless, the usual story is persistence of initial lesions or partial clearing with many recurrences throughout the lifetime of a patient, with varying degrees of intensity and involvement.[7]

If psoriasis remains localized without evidence of progression, the patient's normal life is unaffected by its presence. Anxiety over the disease may be nonexistent or overwhelming, depending on a host of factors. The expected favorable prognosis is altered by the complication of arthritis. The arthritis commonly is rheumatoidlike in morphology, but involves primarily the terminal interphalangeal joints along with other small joints of the hands and feet and an occasional large joint. Sometimes the more the cutaneous lesions assume an exudative character, the more extensive and acute the arthritic involvement becomes. Extensive nail involvement is usual in such cases. The exact incidence of arthritis in psoriatics is difficult to determine, a conservative figure being 6 per cent.[19] The disability encountered may be mild to incapacitating.

Another detriment to the psoriatic's well-being is the exfoliative state. If the disease progresses to involve the total body surface, a threat to general health arises. Fortunately this complication is uncommon, occurring in only about 1 per cent of psoriatic patients.[9] This may occur spontaneously or be precipitated by external or internal therapy. Following clearing, exfoliative psoriasis may recur either as an exfoliative state or as the usual psoriatic eruption of limited distribution. Recently, administration of the antimalarial agents Atabrine or chloroquine[18, 20] has been followed by a dramatic flare with progression to an occasional exfoliative psoriatic state.

Illustrative Case Summaries

Case 1. D. L., a 55-year-old housewife, a native of Scotland, at 20 years first had circumscribed, erythematous skin lesions covered with silvery scales over the elbows, knees, and scalp. Her mother had had a similar eruption for most of her adult life. There were no associated symptoms. The patient had lived in England, in Australia, and in the eastern part of the United States. Until the present time, partial remissions had occurred during the summer season; the longest free interval was approximately 6 months. She had been concerned only because of the cosmetic embarrassment. Yearly visits to Florida in midwinter had alleviated the condition somewhat. Many local remedies had been tried; the greatest benefit occurred after the use of a modified Goeckerman regimen. On examination, large erythematous patches covered with silvery scales were found present on the elbows, knees, and shins. Nail and joint involvement were not

present. The patient's blood pressure was 180/100; grade 2 hypertensive retinopathy was present. Her cardiac and renal systems were found to be within normal limits.

Comment. The foregoing case illustrates the usual course of psoriasis beginning in young adulthood and persisting through 35 years, with alleviation in the summer. Its only importance to the patient has been the undesirable cosmetic appearance.

Case 2. T. M., a 25-year-old woman, mother of 3, first noticed moderate swelling and redness of her fingertips in January 1958. Within several days almost all the fingernails and toenails had become involved. At the same time, varying-sized bright red areas appeared on the extensor surfaces of the arms and legs, the suprapubic area, vulva, the gluteal cleft, the umbilicus, and the left breast. Within 24 hours these were covered with a yellow crust which, upon removal, left an oozing surface. A moderate conjunctivitis was present from the time of onset. No arthritic symptoms occurred. Pruritus was present initially, but gradually subsided during 4 weeks in the hospital. The patient had never suffered from any previous skin disease.

Bland topical therapy during the first 2 weeks was given, with a gradual subsidence of the acuteness. The skin lesions became typical psoriatic lesions. Therapy with 3 per cent ichthammol ointment and increasing exposure to ultraviolet light were then instituted.

Three months after onset, all psoriatic areas had either faded completely, leaving only residual hyperpigmentation, or partially, with slight activity in some lesions, especially on the extensor areas of the extremities.

Comment. This patient suffered from an acute eruptive psoriasis in the initial stage. There were no detectable precipitating factors. In the beginning the lesions were atypical. Under conservative topical management an evolution of the lesions to a typical morphology of psoriasis took place. Likewise, the involution of the lesions over a 3-month period, with residual hyperpigmentation followed a usual pattern. The exact future course of this patient's disease is unpredictable.

Case 3. H. S., a 47-year-old man, had the onset of his psoriasis at age 2. During the last 10 years he has had extensive exacerbations, characterized by showers of pustular lesions, particularly on the hands and feet. These are accompanied by low-grade fever. Arthritic symptoms in the small joints of the hands and feet began concurrently and have progressed to the extent that the patient is unable to use his hands. He has been unable to work for the past 5 years.

On examination, the fingers were fixed in flexion, forming a "claw hand." The palms and soles were studded with pustules superimposed on erythematous bases. Greasy, exudative crusts were present at sites of older pustules. The nails were distorted, hyperkeratotic, and crumbling. Extensive trunk and scalp lesions were not sharply demarcated, but also were quite exudative and inflammatory, presenting an eczematoid appearance. Laboratory studies were within normal limits. On several occasions *Staphylococcus aureus* was cultured from his pustules. The patient's course has been essentially unaltered by removal of diseased teeth and by the administration of

corticosteroids and antibiotics. He continues to be a semi-invalid without any prospect of recovery from his disease.

Comment. This patient presents a true pustular psoriasis accompanied by arthritis of the hands and feet. His disease process incapacitates him almost completely. Pustular psoriasis often is less severe than in this man, whose illness did not respond to any type of therapy. Furthermore, his emotional outlook has been depressed.

Case 4. T. S., a 56-year-old man, had had psoriasis for 10 years prior to his first attack of a generalized exfoliation in May 1956. This attack was preceded by an undetermined type of pneumonia for which he received penicillin. The exfoliative psoriasis subsided somewhat in 6 weeks following corticosteroid therapy, with residual lesions remaining over the elbows, knees, and nails. A second exacerbation of his exfoliative state occurred in September 1956, when cortisone was withdrawn entirely. During this episode a modified Goeckerman regimen resulted in almost complete clearing of his eruption. The patient enjoyed good health for approximately 1 year, when his third exfoliative attack occurred in September 1957. Triamcinolone was administered, with some clearing of his erythroderma, but following withdrawal of this steroid an acute exacerbation occurred, necessitating hospitalization. The patient's entire body was covered with a scaly, dull-red eruption; the nails showed destructive changes. He was emaciated and appeared chronically ill. In the hospital he developed a fulminating staphylococcal pneumonia and coronary thrombosis. After a full trial of appropriate antibiotic therapy without improvement, triamcinolone was given. The immediate response was favorable. During this recovery stage, an activation of an old pulmonary tubercular lesion was discovered.

During the 4-month hospital stay the patient made satisfactory gains. At present he has only a few lesions of psoriasis on his extensor surfaces. However, when attempts are made to reduce the dosage of triamcinolone, new guttate lesions appear in great numbers.

Comment. This patient exemplifies an exfoliative psoriasis with many serious complications, namely, pneumonia (not uncommon in such patients), coronary thrombosis, and activation of latent tuberculosis. These last two are probably related to the corticosteroid therapy. This sequence of events is distressing, and it is a matter of conjecture what the patient's status might have been had he not had a background of exfoliative psoriasis. His prognosis remains guarded.

Case 5. L. J., a 42-year-old single woman, first experienced arthritis and psoriasis at the age of 16 years. Since the onset 26 years ago she has had continuous involvement, with concomitant exacerbations of her skin eruption and arthritis. Since 1950 she has received various types of corticosteroid therapy without any permanent remission, either in the arthritis or the psoriasis. She has developed classic features of iatrogenic Cushing's disease. In 1953 a duodenal ulcer appeared, which healed under a strict medical regimen. On examination, a diffuse involvement with psoriasis over the extremities, trunk, and scalp is present. The small joints of the hands, of the fingers, and the toes are deformed and fixed in extension. Through

perseverance and determination the patient has been able to continue to carry out her housekeeping chores.

Comment. This patient suffers with a chronic, deforming disease that has not been arrested by medical therapy. The simultaneous onset of typical psoriasis and rheumatoidlike arthritis with a parallel course is not uncommon. Although the patient has moderate emotional lability, she has adjusted to her situation in spite of progressive disease.

Summary

Psoriasis is a chronic, occasionally acute, recurrent, inflammatory condition of the skin characterized by round erythematous patches of differing sizes covered by silvery-white scaling. These are distributed symmetrically over the extensor surfaces of the extremities, on the scalp, trunk, sacral area, and the nails. The extent of involvement varies greatly. Morphologic types such as pustular, eczematous, seborrheic, or rupioid lesions are encountered. The onset is usually gradual, but may be acute and exanthematous. The course is inconstant. Remissions occur more frequently in the summer, but the disease usually recurs at some future time.

In the majority of patients the general health remains unaffected. The main complication is a usually rheumatoidlike arthritis of varying intensity in approximately 6 per cent of the patients. Total skin involvement with exfoliation occurs in a very small percentage (1 per cent or less) of psoriatics.

References

1. Andrews, G. C. & G. F. Machacek. 1935. Pustular bacterids of the hands and feet. Arch. Dermatol. and Syphilol. **32**: 837.
2. Anken, G. 1948. Studies on serum lipids and constitutional types of psoriatics and normals. Ejnar Munksgaards Foilag. Copenhagen, Denmark.
3. Barber, H. W. 1930. Acrodermatitis continua vel perstans (dermatitis repens) and psoriasis pustulosa. Brit. J. Dermatol. Syphilis. **42**: 500.
4. Bechet, P. E. 1936. Psoriasis. A brief historical review. Arch. Dermatol. and Syphilol. **33**: 327.
5. Becker, S. W. & M. E. Obermayer. 1947. Modern Dermatology and Syphilology. 2nd ed. : 233. Lippincott. Philadelphia, Pa.
6. Bereston, E. S. 1950. Incidence of psoriasis. Arch. Dermatol. and Syphilol. **62**: 716.
7. Church, R. 1958. The prospect of psoriasis. Brit. J. Dermatol. **70**: 139.
8. Forssman, H. 1947. Frequency of psoriasis among population at large. Acta Dermato-Venereol. **27**: 492.
9. Goeckerman, W. H. & P. A. O'Leary. 1932. Erythroderma psoriaticum. J. Am. Med. Assoc. **99**: 25.
10. Hoede, K. 1957. Zur Frage der Erblichkeit der Psoriasis. Hautarzt. **8**: 433.
11. Ingram, J. T. 1958. Pustular psoriasis. A.M.A. Arch. Dermatol. and Syphilol. **77**: 314.
12. Lane, C. G. & G. M. Crawford. 1937. Psoriasis. A statistical study of two hundred and thirty-one cases. Arch. Dermatol. and Syphilol. **35**: 1051.
13. Lerner, C. 1940. Hereditary influences in psoriasis. J. Invest. Dermatol. **3**: 349.
14. Schamberg, J. F. 1924. The known and unknown about psoriasis. J. Am. Med. Assoc. **83**: 1209.
15. Suskind, R. R. 1954. Eccrine function in psoriasis. J. Invest. Dermatol. **23**: 345.

16. Willan, R. 1801. The Description and Treatment of Cutaneous Diseases. J. Johnson. London, England.
17. Wise, F. & M. B. Sulzberger. 1940. Psoriasis and its treatment. *In* Year Book of Dermatology and Syphilology. : 1–60. Year Book Publ., Inc. Chicago, Ill.
18. Witten, V. H. & M. B. Sulzberger. 1956. Case Report. N. Y. Acad. Med. Section of Dermatol. and Syphilol. A.M.A. Arch. Dermatol. and Syphilol. **73**: 636.
19. Wright, V. 1957. Psoriasis and arthritis. Brit. J. Dermatol. **69**: 1.
20. Ziprkowski, L., S. Haim & H. Bank. 1954. Atabrine in psoriasis. Acta Med. Orient. **13**: 45.

PATHOLOGY OF PSORIASIS

By Elson B. Helwig

Division of Pathology, Armed Forces Institute of Pathology, Washington, D. C.

The histopathological criteria of psoriasis have been defined by several investigators, but proper interpretation of a biopsy specimen to establish this diagnosis may nonetheless be difficult. To illustrate this point I shall discuss my observations on the microscopic changes noted in more than five hundred cases of psoriasis.

Some of the specimens were taken to demonstrate the various stages or types of lesions of unquestionable psoriasis, but many were submitted for what diagnostic aid microscopic examination might offer. Included were specimens from twenty patients who ultimately came to autopsy. Most of the tissues were fixed in formalin, but occasionally in other fixatives, and fresh tissue was available in a few cases. Sections stained with hematoxylin and eosin were prepared routinely. In selected examples, sections were stained by the following methods: Snook's reticulum, periodic acid-Schiff with and without digestion with diastase, Weigert's elastic, van Gieson's, acid mucopolysaccharide with and without digestion with hyaluronidase, and oil red O. A few fresh tissue sections were stained for alkaline phosphatase. Numerous examples of localized and generalized neurodermatitis, contact dermatitis, and mycosis fungoides, and several examples of seborrheic dermatitis and of the recalcitrant pustular eruption were available for comparative purposes.

The early lesion. The earliest lesion studied was of two days' duration. The epidermis exhibited mild acanthosis, some irregular decrease in the granular layer, and slight hyperkeratosis with a minute parakeratotic scale. The stratum corneum showed incomplete separation with an air space between the lamina. The acanthosis appeared to involve the entire epidermis, and the rete ridges were plump, short, and fairly uniformly spaced. There was no disposition to thinning of the epidermis over the papillae. Over some papillae the epidermis showed distinct spongiosis, but elsewhere the prickle cells appeared normal. Microabscesses of Munro were not noted. A few mitotic figures were seen near the basal cell layer. The connective tissue papillae were distinctly edematous and contained a few lymphocytes, monocytes, and swollen fibroblastic cells. The capillary endothelium was swollen, but the lumens were small. Elsewhere the corium appeared normal (FIGURE 1).

By the end of the second week the rete ridges usually, but not always, were considerably elongated. Those that were so elongated reached a fairly constant depth into the corium, but the width of the ridges was not uniform in all specimens. Even at this stage, intercommunication or fusion of the ridges was seen in some specimens. Spongiosis frequently was present in the vicinity of the papillae, where migration of leukocytes through the epidermis tended to occur. Polymorphonuclear leukocytes extended through

the epidermis, reaching their greatest concentration at the keratinized layer or in an imperfectly keratinized lamella of parakeratosis in which microabscesses (Munro) were formed. In general, the granular cell layer was diminished, and a scale of parakeratosis was partially formed. At several sites over the papillae the prickle cell layer was thinned, but the papillae did not jut into the keratin or parakeratin. The papillae were bulbous, sometimes edematous, and mildly infiltrated with lymphocytes and monocytes. Capillary loops of the papillae were dilated and hyperemic. In the upper

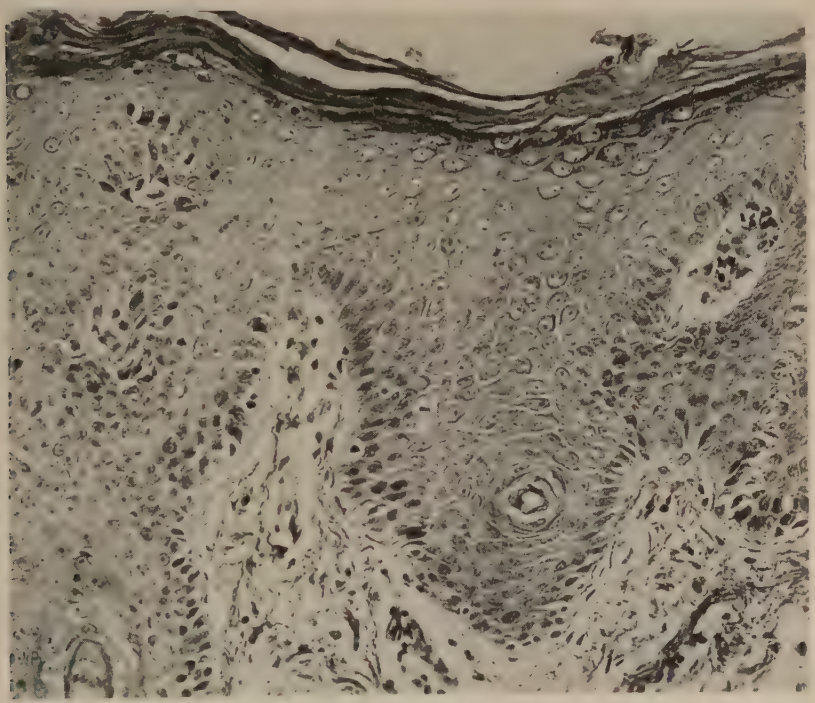

FIGURE 1. Early lesion of psoriasis, showing slight acanthosis, parakeratosis, diminished granular cell layer, and prominent capillaries. ×245. (AFIP Acc. 856634)

corium, capillaries were prominent and surrounded by an edematous reticulum, which was infiltrated with lymphocytes and monocytes.

The established lesion. The diagnosis of a well-established, typical psoriatic lesion can be made rather easily on the basis of a profile of the microscopic changes. However, I have observed considerable variation in this profile, and many lesions are not typical histologically. Acanthosis of the epidermis ranges from mild to marked, and the particular expression of this change is elongation of rete ridges, which is usually minimal in a quiescent lesion, but may be marked in an active lesion (FIGURE 2). There is a general, but seldom precise, uniformity in the depth of the extension of the ridges, and often no appreciable uniformity in their width. In some instances the ridges

are of uniform shape but, judging from my material, this is the exception rather than the rule. More often the ridges vary in width and may exhibit fusion or intercommunication (FIGURE 3).

If the lesion is in an active stage, mitotic figures are common in the epidermis, particularly near the marginal basal cell layer of the rete ridges (FIGURE 4). In a well-established lesion there is little or no melanin pigment in the basal cell layer or throughout the epidermis. However, granules of melanin may be present within melanophages in the corium, where the pigment apparently remains for some time.

FIGURE 2. Established lesion, showing acanthosis with elongation of rete ridges and absence of the granular cell layer. ×91. (AFIP Acc. 290551)

Microabscesses of Munro form in the upper zone of the prickle cell layer by the migration of polymorphonuclear leukocytes through the epidermis. The migration usually occurs over a connective tissue papilla, but at times rete ridges are involved (FIGURE 5). The leukocytes in the deeper zones of the epidermis are seldom distorted, but those in the upper part of the prickle cell layer are beginning to degenerate. Leukocytes in migration are never as concentrated as they are at the site of an abscess, which suggests some attraction for the leukocytes at this point. As the abscesses of Munro are carried upward in the stratum corneum or in a parakeratotic lamella, the leukocytes appear shrunken and pyknotic. Microabscesses may be few, and it may

be necessary to examine numerous sections before one is found (FIGURE 6). In fact, they are not seen in every case. Because of this and the fact that they are observed in other skin diseases such as neurodermatitis and eczematoid dermatitis, they are not diagnostic of psoriasis, but merely an auxiliary diagnostic feature. In pustular psoriasis of the hands and feet the microabscesses usually are fairly large and affect both the prickle cell layer and the stratum corneum. The characteristic acanthosis may not be present in pustular psoriasis, and the changes are difficult to differentiate from those observed in recalcitrant pustular eruption.

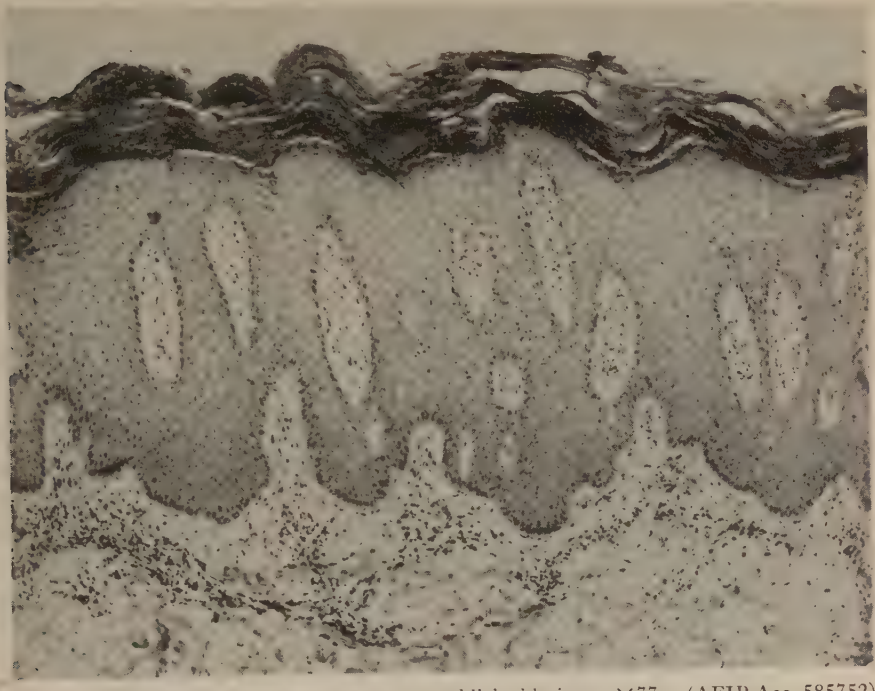

FIGURE 3. Fusion of the rete ridges in an established lesion. ×77. (AFIP Acc. 585752)

The granular cell layer of the epidermis is generally diminished, although this change may be incomplete or irregular in distribution. Above areas where the granular cell layer is absent, the squamous cells retain their nuclei (parakeratosis). The parakeratotic material is intermingled with a hyperkeratotic scale, and often an intervening plate of parakeratosis is sandwiched between two layers of keratin. This particular arrangement has been interpreted as indicative of phases of activity (parakeratosis) and inactivity (normal cornification) in the process.[1] In a classic lesion the parakeratosis is fairly uniform across the epidermis, a feature useful in arriving at a correct diagnosis. If care is not exercised in taking a biopsy specimen, the parakeratotic scale, which is an important diagnostic criterion, will be dislodged,

which makes the diagnosis more difficult (FIGURE 7). The thickness of the scale varies greatly from lesion to lesion, probably as a result of previous treatment or scrubbing of the area. The thickest and most characteristic scales observed in our material were in a number of untreated lesions removed at autopsy. In contrast, other lesions selected at autopsy exhibited only mild acanthosis and a thin layer of keratin with a few parakeratotic lamellae.

FIGURE 4. Mitotic figures in rete ridges. ×530. (AFIP Acc. 585752)

Undoubtedly the latter lesions were quiescent, since there were also fewer microabscesses, no mitotic activity in the epidermis, less capillary dilatation, and a minimal inflammatory cell infiltrate in the corium.

Important changes may occur in the dermis as well as in the epidermis. The connective tissue papillae elongated as the rete ridges increased in length. In this mutual expansion, the tips of the papillae often appeared swollen, and the bases appeared compressed by the widened rete ridges. This appearance, however, was by no means constant; the width of the

papillae and rete ridges often varied considerably, or the papillae were encompassed by fused ridges. The swelling of the tips of the papillae sometimes appeared to be due to edema, but in most instances the stromal cells were increased in number. In PAS preparations no positive-staining material was seen in this area. Stains for acid mucopolysaccharide demonstrated

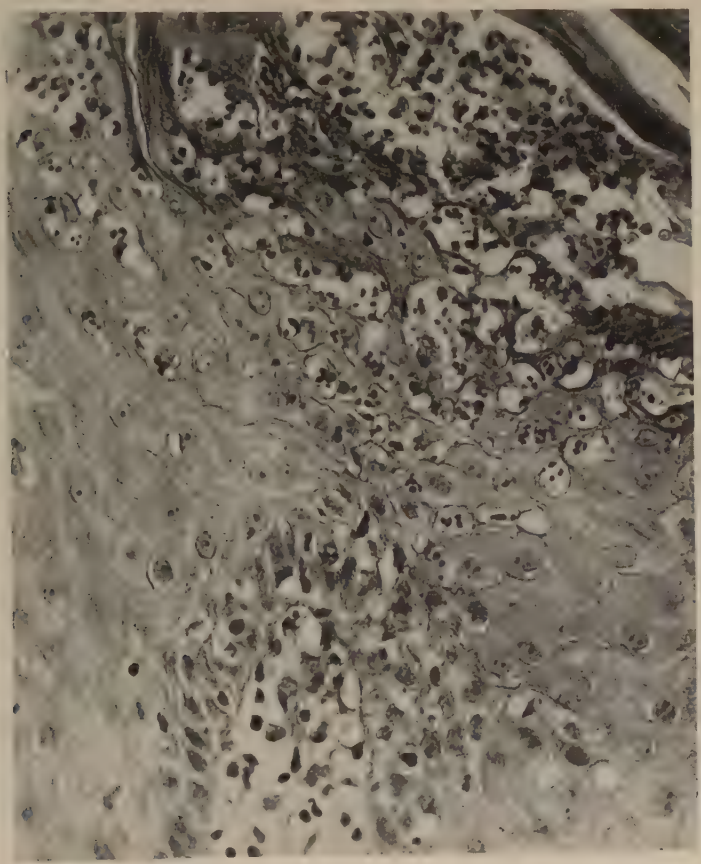

FIGURE 5. Migration of leukocytes from a papilla through the epidermis to form microabscess. ×395. (AFIP Acc. 592262)

a few positive granules and shreds that were resistant to digestion by hyaluronidase. With elastic tissue stains an absence of fibers was seen in the papillae, but they were distributed normally elsewhere in the corium. The reticulum in the edematous papillae was widely separated, but otherwise was normal in distribution. In frozen sections stained with oil red O no increase in the lipid content of the skin could be discerned.

Vascular changes. The capillaries of the papillae were dilated in varying degree, but this change was not observed in each papilla in a single section. In early lesions the endothelial cells were swollen, but in older lesions the

cells were flat. The capillaries of the papillae in well-established lesions tended to be hyperemic and tortuous, with a prominent capillary loop. Over some of the dilated capillary loops in the papillae, the epidermis was only one or two cells in thickness; in other words, the epidermal plate over the connective-tissue papillae was extremely thin (FIGURE 8). In life, when this epithelial plate is removed, the capillaries are a source of bleeding. In addition, it is interesting to note that in some examples, particularly those covered with thick scales, the capillary loops, with a surrounding veil of thin stroma,

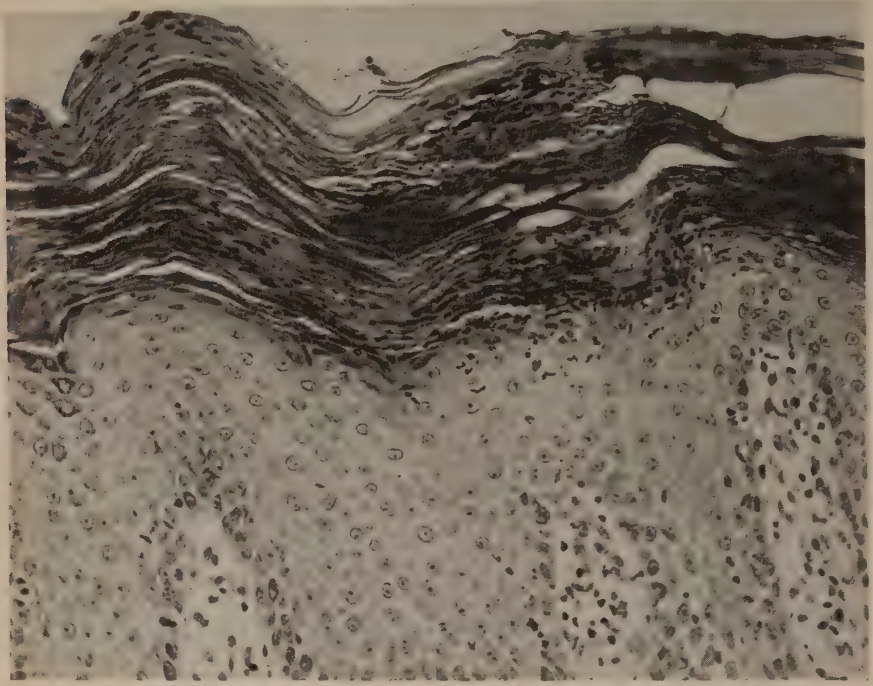

FIGURE 6. Layers of parakeratosis containing microabscesses. ×210. (AFIP Acc. 585752)

jut out into the scale, sometimes far above the normal level of the rete Malpighii. Apparently this represents the pellicle of Buckley, and in my experience this change has not been observed in other dermatoses.[2] Unfortunately, this change was not seen in many of my biopsy specimens and never in those in which the diagnosis was controversial. Stains for alkaline phosphatase, both in early and well-established lesions, demonstrated a normal amount in the capillary walls. In some of the older lesions a pale acidophilic hyalin surrounded the wall of the capillary loop. This substance has not been further identified.

Davis and Lawler[3] examined psoriatic lesions by direct microscopy and reflected light after repeated applications of cellulose tape had removed the keratin layer. In direct visualization of the vessels, they observed that the

end capillaries were extremely tortuous, but that dilatation was not a prominent feature. There was no increase in the number of capillaries, and the capillaries could be seen to pulsate. The capillary pattern was the same in the various types of psoriasis. Examination of normal skin in patients with psoriasis did not reveal a diagnostic abnormality of the capillaries, although a tortuous capillary occasionally was noted, especially in the nail folds (M. Davis, personal communication).

The inflammatory infiltrate. The inflammatory cell infiltrate was of two types. One consisted of polymorphonuclear leukocytes. When present,

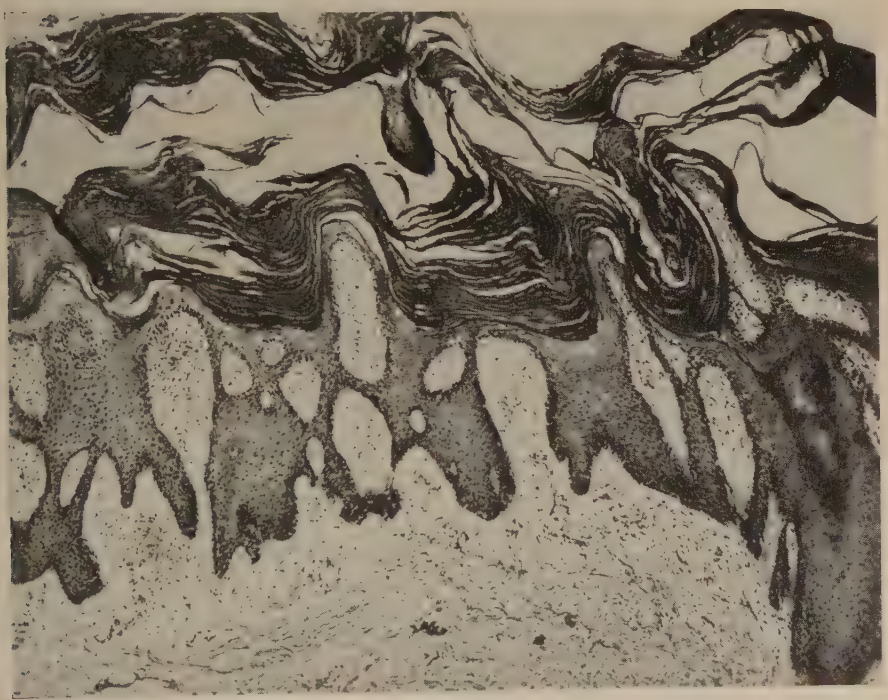

FIGURE 7. Fused and irregularly enlarged rete ridge covered by a thick laminated parakeratotic scale. ×55. (AFIP Acc. 311429)

it was located primarily in the tips of the papillae and served as the source of the leukocytes that migrated through the epidermis to form abscesses of Munro. The other consisted chiefly of lymphocytes and scattered monocytes and was located, for the most part, in the base of the papillae and the upper portion of the corium. Inflammatory cells were noted neither in the deeper corium nor the subcutaneous fat. Plasma cells were rare, and eosinophilic leukocytes were absent. Mast cells usually were present, but were not numerous (FIGURE 9).

So-called aberrant lesions. A fair proportion of the biopsy specimens from cases of psoriasis received at the Armed Forces Institute of Pathology did

not show the classic histological pattern of the disease. Some of these undoubtedly represented so-called aberrant lesions of psoriasis. In general, the acanthosis tended to be somewhat more irregular, and spongiosis and even small vesicles were seen relatively often at the surface of the scales. Thinning of the epithelial plates was less marked, and capillary loops were not prominent. By accepted criteria and standard techniques it is impossible to make a firm interpretation of these lesions as psoriasis; they can only be called "psoriasiform" or "consistent with psoriasis" on the basis

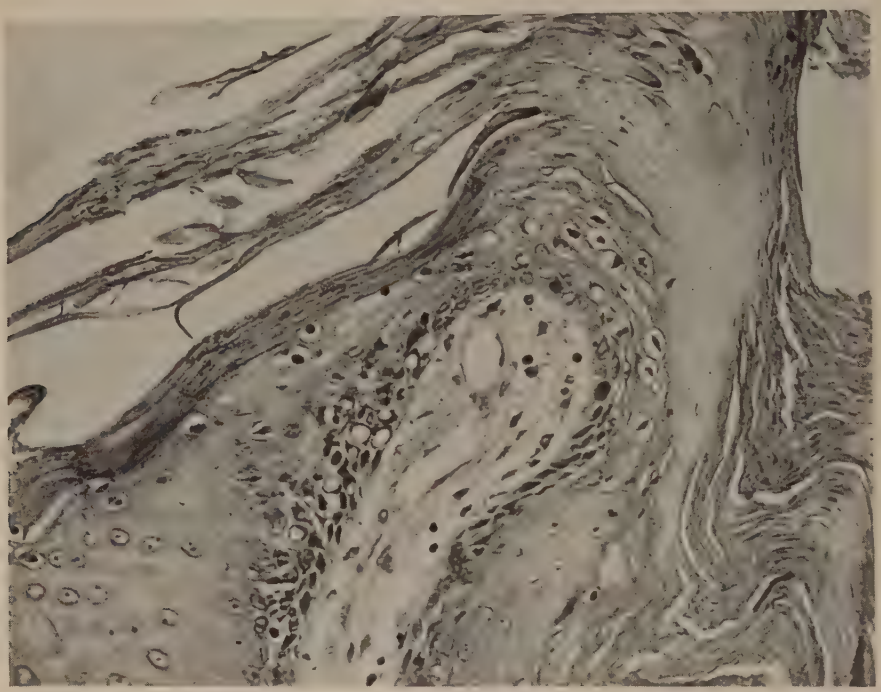

FIGURE 8. A field from FIGURE 2, showing thinning of the epithelial plate over a papilla and a tortuous capillary. ×245.

of the histological changes. In exfoliative psoriasis the changes are essentially those of psoriasis.

Penile lesions. There were twelve biopsy specimens from the penis. As a group, these were most difficult to diagnose histologically as psoriasis. The acanthosis was often irregular; usually only a thin keratotic-parakeratotic scale was present, and frequently the capillaries of the irregularly shaped papillae were not greatly dilated.

Histological characteristics of lesions obtained at autopsy. Most of the twenty patients who came to autopsy had had psoriasis for many years. All but one of the patients were men. In several patients, specimens of the skin lesions taken during life and at autopsy revealed much the same histo-

logical variations I have described. A few sections taken at autopsy were from dermal lesions that apparently had not been treated, or at least not recently. The epidermis was covered by a thick keratotic-parakeratotic scale, and the papillary capillaries jutted strikingly into the scale. The cause of death of these patients was varied, but it is interesting to note that three of them had portal cirrhosis and five had arthritis. No consistent change was observed in the viscera or endocrine glands.

Histological differential diagnosis. Other lesions may be confused histologically with psoriasis.[4] Perhaps the one causing the most difficulty in my

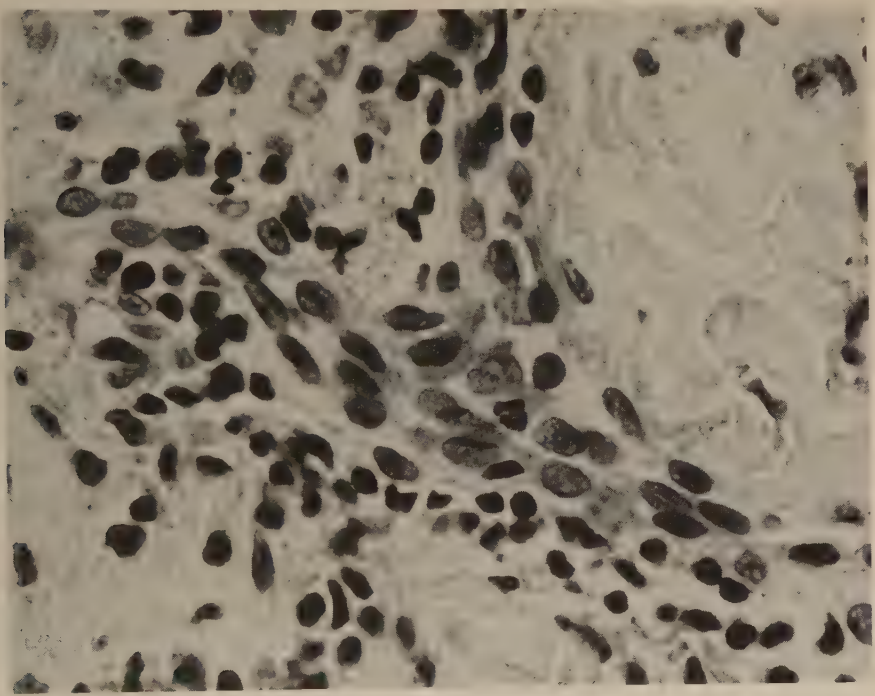

FIGURE 9. Inflammatory infiltrate, predominantly lymphocytic, at the base of a papilla. ×790. (AFIP Acc. 585752)

experience is lichen simplex chronicus. In the lesions of that disease there is an acanthosis that differs by its greater irregularity from that seen in psoriasis. However, any given field may look like psoriasis. The granular cell layer may be diminished or absent; parakeratosis and even microabscesses may be present. Such minor aspects as the presence of spongiosis, lack of dilatation of the capillary loops in the papillae, and a denser and more widespread inflammatory infiltrate in lichen simplex chronicus may be the only differentiating features. The infiltrate, in addition to lymphocytes and monocytes, may contain plasma cells and eosinophilic leukocytes. I must admit that there are times when I cannot tell by the histological appearance whether the lesion is psoriasis or lichen simplex chronicus. Eczematoid

dermatitis is another lesion which may look like psoriasis histologically. Marked spongiosis and eosinophilic leukocytes in the inflammatory infiltrate, when present, favor the diagnosis of eczematoid dermatitis.

Comments. Approximately five hundred histological specimens of psoriasis were studied. Some of these specimens were selected specifically to show certain stages or types of psoriasis, but most of them presented problems in histological diagnosis. It is commonly accepted that the diagnosis of psoriasis can be made rather easily on the basis of a combination of microscopic changes.[5, 6] These criteria include regular acanthosis with elongation of the rete ridges, a diminished granular cell layer, layered parakeratosis, mitotic figures in basal and lower prickle cells, papillomatosis with clubbing of the papillary bodies, thinning of the epidermis over the papillae, tortuous and dilated capillary loops in the papillae, microabscesses of Munro, and a mild infiltration of lymphocytes and monocytes in the upper corium.

In my material, many of the lesions were readily interpreted as psoriasis by these criteria. In contrast there were a substantial number of lesions in which the histological profile did not fulfill the accepted criteria, and a clear-cut diagnosis of psoriasis could not be made. This group of cases probably included examples of the aberrant forms of psoriasis reported by MacKee and Foster.[7] These authors believed that psoriasis could not be unequivocally diagnosed from observation of a histological section without a consideration of clinical features. Furthermore, they considered the aberrant lesions as linking psoriasis through a common etiological factor to seborrheic dermatitis and neurodermatitis. It is also conceivable that, in these diseases, different etiological factors may affect the skin in a way that would produce similar lesions, since this organ has a limited way of response. Madden[8] studied uninvolved skin of patients with psoriasis and saw histological changes that simulated those of a psoriatic lesion. I have been unable to confirm this observation.

On the basis of this histological material it is impossible to determine whether the initial affection is in the epidermis or dermis. However, in the earliest lesions examined, the capillaries were involved, and it seems entirely possible that the epidermal change is secondary. Furthermore, in many of the lesions, pericapillary edema about the loops, at some stage, is out of proportion to the inflammatory cell infiltrate and is probably the result of an unknown reaction. At other stages, polymorphonuclear leukocytes invade the papillary bulb and migrate to the surface of the epidermis, where they collect in small abscesses. There must be a leukotactic factor at this site, but it cannot be decided whether it is a metabolic product of the epidermis, a humoral factor that has reached this point from the capillary loop, or even a change in the electric potential. The mechanism is not unique to psoriasis, since microabscesses of the epidermis occur in other entities.

References

1. Gans, O. 1925. Psoriasis. *In* Histologie der Hautkrankheiten. **1:** 280. Springer. Berlin, Germany.
2. Feit, H. In discussion on MacKee and Foster. : 54.[7]

3. Davis, M. J. & J. C. Lawler. 1958. The capillary circulation of the skin. A.M.A. Arch. Dermatol. **77**: 690–703.
4. Helwig, E. B. 1955. Seminar on the skin, neoplasms and dermatoses. Proc. 20th Seminar Am. Soc. Clin. Pathol. : 29–30.
5. Burk, J. W. & H. Montgomery. 1943. Histopathologic study of psoriasis. Arch. Dermatol. and Syphilol. **48**: 479–493.
6. Civatte, A. 1924. Psoriasis and seborrheic eczema: pathological anatomy and diagnostic histology of the two dermatoses. Brit. J. Dermatol. **36**: 461–476.
7. MacKee, G. M. & P. D. Foster. 1936. Histopathogenesis of psoriasis and its aberrant lesions. Arch. Dermatol. and Syphilol. **34**: 35–56.
8. Madden, J. L. 1941. Histologic studies of uninvolved skin of patients with psoriasis. Arch. Dermatol. and Syphilol. **44**: 655–664.

THE HISTOCHEMISTRY OF PSORIASIS

By O. Braun-Falco

Skin Clinic, Johannes Gutenberg University, Mainz, Germany

In order to gain insight into metabolic functions, it is the task of histochemistry to show the presence of chemical substances in cells and tissues with the use of sensitive methods in histological sections.[88] If one considers the histochemical findings in psoriasis in this light, there is no doubt that many of them can be related to biochemical findings that in recent times have led Rothman,[126, 127] Grüneberg and Szakall,[67] and Flesch and Esoda[55] to newer concepts concerning the keratinization process and the nature of psoriasis.

The histological picture of psoriasis is dominated by a marked acanthosis and parakeratosis with the formation of Munro's abscesses in the epidermis while, in the dermis, an inflammatory process is present, especially in the papillary portions. When discussing the histochemistry of psoriasis, one could use these features as guideposts in an attempt to clarify the nature of the disease. This approach has been followed by Steigleder in his extensive study of the histochemistry of acanthosis[145] and by Braun-Falco,[25] Spier and Caneghem,[140] and Steigleder[149] in their detailed works on parakeratosis. However, for the purpose of the present review, it seems to be more appropriate to divide the material on the basis of the histochemical localization of various chemical compounds within the epidermis and dermis with a brief discussion of their functional significance; our knowledge in this last area is still very scant.

The following topics will be reviewed: (1) the histochemistry of the epidermis in psoriasis, including the histochemical localization of inorganic substances; of carbohydrates; of lipids; of proteins, amino acids, sulfhydryl groups, and nucleic acids; and of enzymes; and (2) the histochemistry of the corium in psoriasis, including that of the basement membrane; of the capillaries; and of the ground substance.

The Histochemistry of Psoriatic Epidermis

Histochemical studies of psoriatic skin lesions are by no means of recent origin. The founder of cutaneous histochemistry, P. G. Unna, made some interesting observations more than a generation ago.[157, 158] A more systematic investigation, however, has been made possible only during the past few years through the introduction of many new methods.

The Histochemical Localization of Inorganic Substances

For studying the distribution of inorganic substances in the epidermis, much use has been made of spodograms,[72] that is, of the pictures of microincinerated skin sections. Although it is impossible to identify with certainty the various components after ashing—iron is an exception[102]—some interesting results still emerge (TABLE 1) from a long series of works.[51, 52, 58, 71,

TABLE 1
HISTOLOGICAL LOCALIZATION OF INORGANIC SUBSTANCES IN NORMAL AND PSORIATIC EPIDERMIS*

Method	References	Normal skin			Psoriatic skin		Remarks
		Epidermis	Transitional zone	Horny layer	Epidermis	Parakeratotic horny layer	
Spodogram							
(1) Total ash	Gans[58] Herrmann[71] Kruse[80]	+	Not increased	+	+++	+++	
(2) Ca salts	Gans[58] Engman & McCardle[61]	+	Not increased	+	+++	+++	
(3) Mg salts	Kruse[80] Engman & McCardle[61]	+	Not increased	+	+++	+++	
(4) Fe salts	Kruse[80] Engman & McCardle[61]	+	Not increased	+	++/−	−	
Spectrogram Cu	McCardle *et al.*[92]	+	−	−	+++	−	
Histochemical Zn	Braun-Falco & Rathjens[38]	++	−	+/−	+/−	−	Possible imbibition of surface by Zn from sweat, etc., as a source of error

* Literature cited refers to changes in psoriasis.

[78, 124, 125] In psoriatic lesions the total ash content is increased above normal, especially in the rete pegs and the lower stratum spinosum.[58, 71] An increased ash content, probably mainly of Mg salts, was found also in the psoriatic horny layer.[80] The high ash content of the psoriatic epidermis may be due to an enrichment in calcium salts, according to Gans.[58] Together with an increase in calcium and magnesium, Engman and McCardle describe an increase in iron; this finding is in contrast to other inflammatory dermatoses, such as lichen planus or chronic dermatitis.[51] According to Kruse, however, the iron is decreased in the psoriatic epidermis.[80] Microspectrographic analyses revealed a normal magnesium and a markedly elevated copper content.[92] This high copper content, if confirmed, could be of great interest in view of the specific, catalytic role of copper in the formation of disulfide bridges during keratinization.[126, 127] The increased rate of keratinization in psoriasis may be related to the high copper content.

To the best of my knowledge there are no radioactive studies in psoriasis such as have been carried out with radioactive Ca^{45} in animal skin.[8]

The high mineral content of the psoriatic epidermis is of special interest because, in experimentally induced hyperplastic animal epidermis, the amounts of minerals are decreased.[83] Also in hyperplastic and precancerous human epidermis the dry weight, as determined with radioautography, is reduced as compared with normal specimens.[99]

Braun-Falco and Rathjens tried to estimate zinc in the skin with a modified dithizon technique, in order to establish the possible role of this element in the pathogenesis of parakeratosis. All epithelial structures give a consistently positive cytoplasmic reaction.[37] This is not surprising, because zinc is not an inactive storage element of the skin,[49] but has an important role as a cofactor in a number of enzymes.[126] Zinc deficiency in the rat causes parakeratosis and follicular atrophy;[57] in the swine it causes a disease called parakeratosis, which resembles psoriasis not only clinically but also histologically.[76] In contradiction to a previous report,[92] in our own studies with dithizon we found a markedly decreased reaction in the acanthotic epidermis of psoriatics, as compared with normal skin and with other inflammatory dermatoses.[38] These semiquantitative results should be confirmed with quantitative chemical methods. There is no proof, however, that psoriasis is a simple zinc deficiency; in our preliminary clinical tests, internal administration of zinc sulfate had *no* therapeutic effectiveness.

The Histochemical Localization of Carbohydrates

Among the carbohydrates, the histochemical localization of glycogen in normal and pathological epithelial structures has been subjected to the most thorough studies.[15, 152] These studies have received a considerable impetus since the introduction of the periodic acid-Schiff (PAS) reaction by McManus.[93, 94] When used with proper tissue fixation, this method is ideally suited for the demonstration of polysaccharides. Glycogen may be identified through its digestibility by diastase or saliva. There are several reviews on the mechanism of action and on the specificity of the PAS reaction.[15, 30, 61, 89, 115]

In the first fetal months the epidermal cells contain abundant glycogen in their cytoplasm; the adult epidermis is usually devoid of glycogen, except for occasional small amounts in the stratum spinosum. In the acanthotic epidermis of psoriatics, abundant glycogen was described as early as 1921.[132] Numerous authors studied the histochemical localization of glycogen with the PAS reaction.[14, 15, 109, 128, 144, 152] In all these studies, glycogen has been reported to occur most copiously in the central parts of the hypertrophic rete pegs. On the other hand, Braun-Falco could find only occasional glycogen in the Malpighian layer above the apices of the papillae; the cells of the basal layer were always free of glycogen.[15] In contrast to Steiner,[152] we found glycogen only exceptionally in the parakeratotic horny layer.

The increase of glycogen, an important source of energy, is quite characteristic of psoriasis, but by no means specific. Its significance is obscure.

The elevated glycogen in the psoriatic epidermis is not related either to the proliferating capacity of the tissues or to a retarded keratinization.[42, 105] Such an assumption is also disproved by the considerable enrichment in glycogen in cells of atrophic epidermis (for example, chronic lupus erythematosus). Glycogen may be absent in acanthotic epidermis of nonpsoriatic origin (callus, verruca vulgaris, condyloma acuminatum,[152] lichen planus).[15] The function of glycogen is thus not related solely to the degree of acanthosis, to mitotic activity, or to an abnormally increased rate of keratinization.[42, 103-105] Neither does insufficient oxygenation[13] account for the epidermal accumulation of glycogen.[16] The alleged relation between the deposition of glycogen and the type of keratin formed[152] (much glycogen in parakeratosis, little glycogen in hyperkeratosis) has no validity, either. With histochemical methods abundant glycogen can be demonstrated in the epidermis of some hyperkeratotic conditions (chronic lupus erythematosus, ichthyosis congenita) and around the orthokeratotic horny pearls of squamous cell carcinomas.[15]

In summary, we can state that we do not know the cause of the epidermal accumulation of glycogen in psoriasis or in pathological conditions in general. This accumulation must have its origin in some special circumstance of cellular metabolism. Furthermore, phosphorylase occurs in all noncornified psoriatic epidermal cells.[29] This enzyme is essential for glycogen synthesis. Its presence indicates that all nonkeratinized psoriatic cells have the potentiality of glyconeogenesis. It appears that all histological findings of glycogen in the epidermis in physiological and pathological conditions represent temporary stages that are undoubtedly subject to rapid alterations.

The significance of glycogen as a source of energy is supported, not only by its consistent absence in mitotic cells, but also by observations made on eccrine sweat glands. In their resting phase, these cells contain large amounts of glycogen; this intracellular glycogen disappears during increased activity in the secretory phase.[90, 102, 137, 162] These findings are of interest in connection with psoriasis. In psoriatic lesions the eccrine sweat glands have a diminished secretory activity; the cause of the sweat retention is the plugging of the ducts by parakeratotic material.[155] This decreased activity is reflected in the marked accumulation of glycogen in the cells of the sweat

glands and ducts in psoriasis and especially in psoriatic erythroderma;[15, 45] the glycogen disappears after the injection of mecholyl.[45]

Examination of psoriatic skin sections after they have been incubated with diastase or saliva reveals that, in addition to glycogen, psoriatic epidermis contains still other PAS-reactive substances. This diastase- and amylase-resistant PAS-reactive material is most prominent in the parakeratotic horny layer, in intercellular spaces, and in the sweat ducts; as a rule, the epidermal cells themselves are free of PAS-reactive substances.

PAS-reactive, diastase-resistant material may be diffusely distributed throughout the cells of the granular layer;[15] these substances are also resistant to hyaluronidase and tryptic digestion. The normal or hyperkeratotic horny layers are PAS-negative; parakeratotic horny layers, especially in the absence of an underlying keratohyalin layer, exhibit a more or less pronounced PAS positivity, resistant toward amylase.[14, 15, 149] With special methods, this PAS-reactive material has been identified almost certainly as a carbohydrate.[25] On the basis of its resistance toward testicular hyaluronidase, Murtula[109] believed that these PAS-reactive, saliva-resistant substances could be identified as chondroitin sulfate B. In my opinion, this conclusion is not warranted, since it has been definitely established that neither hyaluronic acid nor chondroitin sulfuric acid are PAS-positive.[15, 30]

It is possible that the PAS positivity is partly due to the presence of increased pentoses in the horny layer;[40, 56, 67] these may originate from the decomposing nuclei of leukocytes in Munro's abscesses or from cytoplasmic ribonucleic acid of epidermal cells. In any case, these PAS-reactive substances are by no means specific for psoriasis. They occur in other parakeratotic dermatoses, occasionally also in normal keratinization when the underlying keratohyalin layer is absent.

In all likelihood this PAS-positive material in the horny layer is related to the stratum granulosum. Whenever the granular layer is properly developed, the horny layer is devoid of PAS-reactive, diastase-resistant substances.[15] In the absence of the granular layer, however, as in the parakeratotic psoriatic epidermis, the parakeratotic stratum corneum contains homogeneously staining PAS-positive material. It must be emphasized that this material should not be mistaken for PAS-positive components of serum that are always distributed in foci throughout the parakeratotic horny layer in psoriasis and stain with PAS more strongly and with a purplish color.

Several authors have described PAS-reactive, diastase-resistant substances in the intercellular spaces of the epidermis, especially on the cell surfaces, in the intercellular bridges, and in Bizzozero's nodes.[15, 48, 120] This material is also resistant to digestion with testicular hyaluronidase and streptokinase and does not exhibit any metachromasia either before or after incubation with these enzymes.[15] The material is probably a neutral carbohydrate compound of obscure significance. This assumption is supported by some of our own unpublished observations. When skin sections are treated with polyvinylsulfonic acid, the carbohydrates become esterified and, after subsequent thorough washing, exhibit metachromasia. Under these

conditions in psoriasis strongly positive reactions are obtained in the intercellular spaces.

The histochemical behavior of this material strikingly resembles that of the homogeneous portion of the basement membrane.[15] The substance is without question not merely a dead cementing matter but a physiologically important substance, as will be discussed later. It appears to be definitely increased in the spinous cell layer of the psoriatic epidermis.[15] Frequently the cell membranes of the parakeratotic horny layer also show an exceedingly strong PAS reaction and amylase resistance. The problem of whether these substances are related to the PAS-positive components in the parakeratotic horny layers of psoriatics has not yet been investigated.

Mention also should be made of a homogeneous PAS-positive, diastase-resistant material present in high concentrations in the cuticle of the epidermal eccrine sweat duct units of psoriatics[45] and, especially, of a similar substance in the lumen of the sweat ducts, mainly in their epidermal portion.[15, 45] Sometimes this substance diffuses into the surrounding keratinous ring. Its precise nature and origin are unknown. Acid mucopolysaccharides probably do not take part in its composition, because it does not stain metachromatically.[45] Occurrence of the substance is not specific for psoriasis, because we have made similar observations in the skin of infants a few days old.

When normal skin is studied with the Hale-PAS or Alcian blue method, it is surprising to find Hale-reactive substances in the intercellular spaces of the epidermis. These substances, which react like mesenchymal acid mucopolysaccharides and show no metachromasis, disappear with increasing keratinization. Their chemical nature has not been elucidated. They are probably epidermal acid mucopolysaccharides. Recent works by Pinkus[116] and Braun-Falco[28] dealing with the syndrome of mucophanerosis intrafollicularis et seboglandularis have proved that under pathological conditions such substances may be liberated in large quantities in epidermal structures. In psoriasis, too, there are numerous Hale- and Alcian blue-positive substances in the frequently enlarged intercellular spaces. Sometimes even the membranes of the horny cells show intensive positive staining. Unfortunately, the specificity of the Hale and Alcian blue methods is limited[31] and therefore it is not definitely permissible to conclude that these reactions prove the presence of acid mucopolysaccharides in the epidermis and in the parakeratotic horny layer. In any case, these findings are of interest in view of Allegra's observations;[1] this author found in psoriasis an increase of metachromatic acid mucopolysaccharides (hyaluronic acid and chondroitin sulfuric acid). From psoriatic scales, Roe has also isolated a water-soluble metachromatic protein of unknown nature[56] (TABLE 2).

The Histochemical Localization of Lipids

In spite of great efforts, not much progress has been made in the field of lipid histochemistry, and many of the methods are inadequate for the differentiation of lipids.[87]

TABLE 2
HISTOCHEMICAL LOCALIZATION OF CARBOHYDRATES IN NORMAL AND PSORIATIC EPIDERMIS*

Method	References	Normal skin			Psoriatic skin		Remarks
		Epidermis	Transitional zone	Horny layer	Epidermis	Parakeratotic horny layer	
Glycogen (PAS reaction)	Sasakawa[132] Braun-Falco[15] Sacchi[128] Steigleder[144] Steiner[152]	+/−	−	−	++/+	−	Rarely, scattered glycogen granula in parakeratotic horny layer
PAS reactive, diastase-resistant substances (carbohydrates)	Braun-Falco[15] Steiner[152] Braun-Falco[14] Braun-Falco[25]	−	−	−	−	+++	Caution! False positive results from coagulated serum
(1) Acetylation-PAS	Braun-Falco[25]	−	−	−	−	−	Blocks all OH and NH_2 groups
(2) Acetylation-KOH-saponification-PAS	Braun-Falco[25]	+	−	−	−	+++/++++	OH-groups for PAS reaction released, NH_2 groups remain blocked: no hydroxy amino acids
Hale-PAS reaction (acid substances, partly mucopolysaccharides, are Hale-reactive)	Braun-Falco, 1957, unpublished	Hale-positive intercellular spaces	Hale-positive keratohyalin granules	Hale −/+	Increased Hale + material in intercellular spaces	Hale+++ } PAS+++ }	The two reactions may be superimposed in the parakeratotic horny layer
Toluidine blue pH 5.0	Braun-Falco, 1957, unpublished	++ orthochromatic	++ orthochromatic	−	++ orthochromatic	++ orthochromatic	Parakeratotic horny layer strongly basophilic

* Literature cited refers to changes in psoriasis.

The cellular lipids are integral constituents of the protoplasm and, like all other organs, the skin and the epidermis with its appendages contain significant quantities of cellular lipids. Most of the time these lipids cannot be identified with the standard fat stains because they are not free, but in a "masked" form, bound to proteins. Under physiological conditions during the process of keratinization they are apparently released from their combination in the keratogenous zone. In this transitional zone,[25] between the stratum granulosum and stratum corneum, there are fatty substances that stain with Baker's acid hematein (phospholipids), FIGURE 1; Fischler's reagent (fatty acid), FIGURE 2; Lillie's performic acid-Schiff reaction (C=C bonds, unsaturated lipids); and the UV-Schiff reaction[9] (unsaturated lipids),[25] FIGURE 3, while the stratum corneum, with the exception of its surface, reacts negatively (TABLE 3). Lipophanerosis can be produced artificially by splitting the lipid-protein complexes through the destruction of the protein components (through tryptic digestion).[121] It is probable that under pathological conditions a similar "unmixing" *in vivo* may give rise to the "appearance" of lipids in the cells.

It has been known for a long time that considerable quantities of lipids are present in the psoriatic epidermis.[75] Von Kerckhoff described especially high concentrations in the basal cells; according to him, these were decreased in the spinous cells and reappeared in the horny layer.[75] However, in Steigleder's findings, the distribution is by no means so regular.[143] Grütz[68, 69] assigned psoriasis to the group of lipoidoses with disturbed cholesterol metabolism ("an epidermal lipoidosis, so to speak"). He distinguished two types: (1) a form with diffuse excretion, characterized by an over-all distribution of lipids in the papillae, from which the lipids reached the intercellular spaces of the epidermis to be eventually cast off with the horny layer; and (2) a corpuscular excretory type in which macrophages loaded with lipids, the so-called lipophages, enter the epidermis from the papillary layer of the dermis. Other investigators have made similar observations.[46, 47] During the demonstration of succinic dehydrogenase with tetrazolium salts the red monoformazans are dissolved in the tissue lipids and give rise to pictures,[36] similar to those described by Grütz.[68] Some negative findings[43] may be due to technical errors.[143] In recent investigations with the use of the Sudan black B technique (FIGURE 4) Steigleder[143] and Dogliotti[47] could fully confirm Grütz's observations.[68] Comparative studies yielded negative results in lichen planus, diffuse neurodermatitis, and granuloma annulare; however, seborrheic dermatitis gave a histological picture analogous to that found in psoriasis.[47] Under experimental conditions with histochemical techniques (Sudan black B), Midana and Dogliotti[97] studied the uptake of various lipids such as cholesterol, olive oil, and lanolin, that were introduced intradermally. They came to the conclusion that, regardless of the type of fat administered, the lipids were taken up by the reticulohistiocytes ("lipophages") and transported into the epidermis; this transport occurred considerably faster and to a greater extent in the normal appearing skin of psoriatics than in the skin of nonpsoriatics.[148] However, Steigleder could not find that the histologically demonstrable epidermal lipids in any way

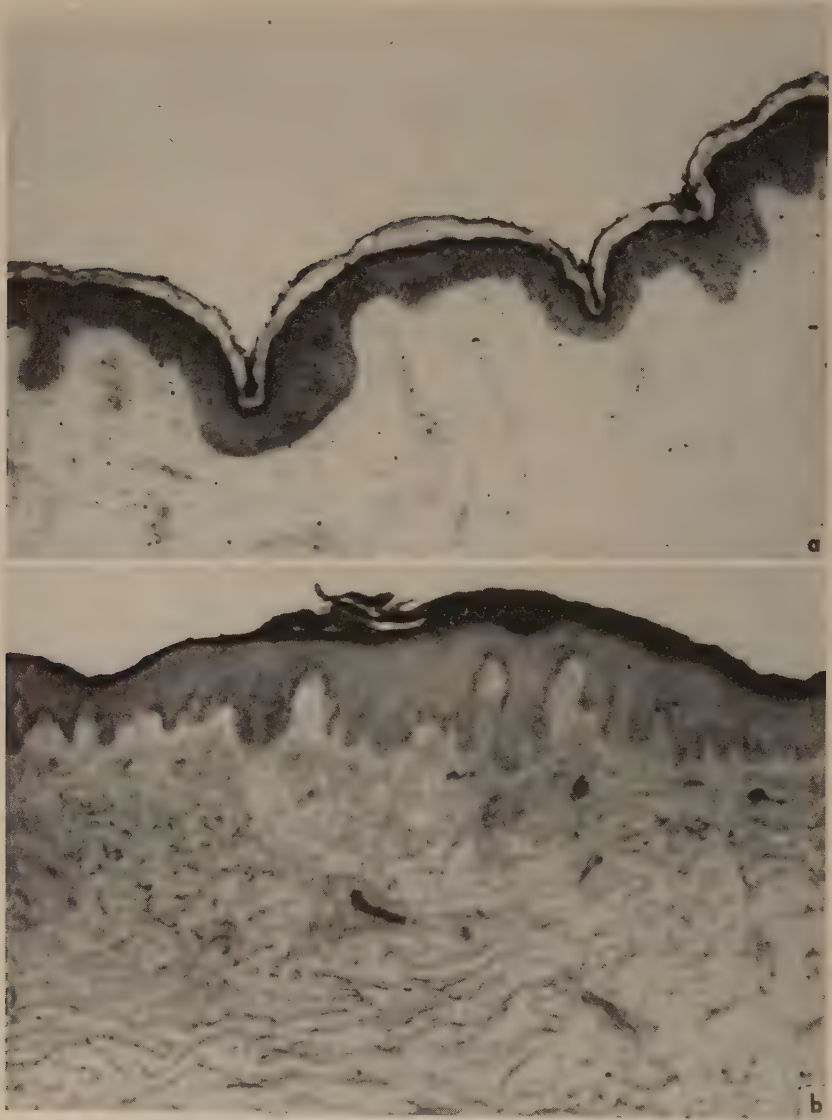

FIGURE 1. Baker's acid hematein for localizing phospholipids. (a) Normal skin, showing intensive positive reaction in the subcorneal transitional zone, negative horny layer, and positive reaction on the skin surface due to surface phospholipids. (b) Psoriatic skin, showing intensive positive reaction throughout the entire parakeratotic horny layer.

FIGURE 2. Fischler's reaction for staining fatty acids. (a) Normal skin, showing intensive positive reaction in the subcorneal transitional zone, negative horny layer (with the exception of a few cells), and positive reaction on the skin surface. (b) Psoriatic skin, showing strong positive reaction throughout the entire parakeratotic horny layer.

reflected the loading of the body with olive oil or cholesterol. He also described psoriasislike features in other dermatoses (scleroderma, diffuse neurodermatitis, mycosis fungoides) with an exocytosis of lipophages;[143] therefore these findings are not characteristic for psoriasis and are of no special importance either from a diagnostic or pathogenetic point of view.

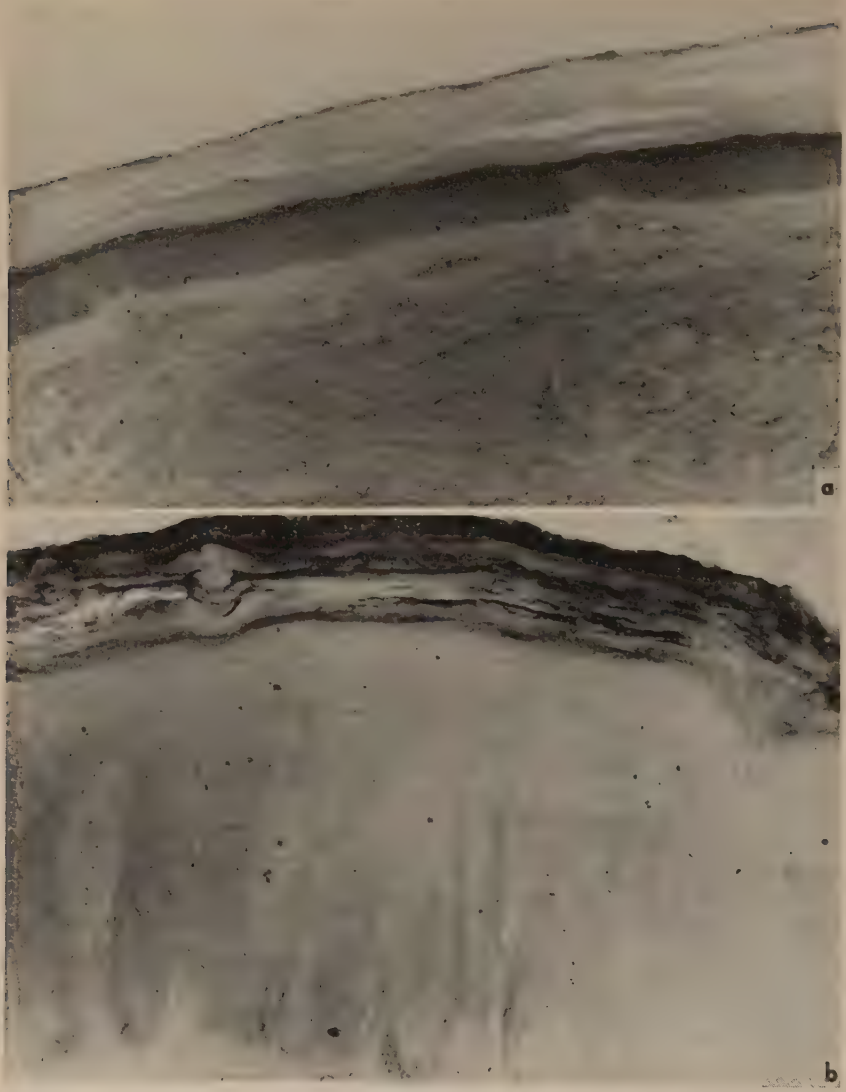

FIGURE 3. UV-Schiff reaction for staining unsaturated fatty acids and lipids. (a) Normal skin, showing intensive positive reaction in the subcorneal transitional zone, negative horny layer, and positive skin surface. (b) Psoriatic skin, showing marked positive reaction throughout the entire horny layer.

Studies with Feulgen and Voit's plasmal reaction have been carried out by Bandmann and Spier.[4] According to them plasmalogen in the stratum Malpighii is rather diminished when compared to that in normal skin, while the parakeratotic horny layer reacts negatively. In our own observations, the plasmalogen content of the epidermis showed wide individual fluctu-

TABLE 3
HISTOCHEMICAL LOCALIZATION OF LIPIDS AND OTHER FATTY SUBSTANCES IN NORMAL AND PSORIATIC EPIDERMIS*

Method	References	Normal skin			Psoriatic skin		Remarks
		Epidermis	Transitional zone	Horny layer	Epidermis	Parakeratotic horny layer	
Sudan black B (lipids)	Steigleder[143] Dogliotti[47]	−/+	+++	−/+	+	+++	Occasional positive reaction on normal skin surface (sebum)
Fischler reaction (fatty acids?)	Braun-Falco[25]	−/+	+++	−	−/+	+++	Occasional positive reaction on normal skin surface (sebum)
UV-Schiff reaction (unsaturated fatty acids)	Braun-Falco, 1957, unpublished	−/+	+++	−	−/+	+++	Occasional positive reaction on normal skin surface (sebum)
Performic acid-Schiff reaction (unsaturated fatty acids)	Braun-Falco[25]	−/+	+	−	−/+	+++	Nuclei are ++
Baker's acid hematein (phospholipids)	Braun-Falco[25]	−/+	+++	−	−/+	+++	
Plasmal reaction (plasmalogen)	Bandmann & Spier[4] and Braun-Falco, 1957, unpublished	+/++ in str. Malpighi	−	−	+/++ in str. Malpighii	−	In Munro's abscesses, leukocytes intensely +
Schiff-reagent free carbonyl groups	Prieto *et al.*[118]	−/+	+++	−	−/+	+++	

* Literature cited refers to changes in psoriasis.

ations, while the parakeratotic horny layer was always negative. On the other hand, the localization of Munro's abscesses was strongly outlined in the parakeratotic horny layer through the excessive plasmalogen content of the leukocytes.

The behavior of the lipids in the parakeratotic horny layer seems to me of special importance. We have already mentioned previous observations concerning the abundant lipid content of the parakeratotic horny layer.[149] A comparison with the normal skin is especially illuminating. In the normal skin phospholipids, unsaturated lipids, fatty acids, and free carbonyl groups occur primarily in the transitional zone underneath the horny layer (TABLE 3). With regard to its lipid content, the parakeratotic horny layer in psoriasis may be considered as an extended transitional zone. It contains lipids

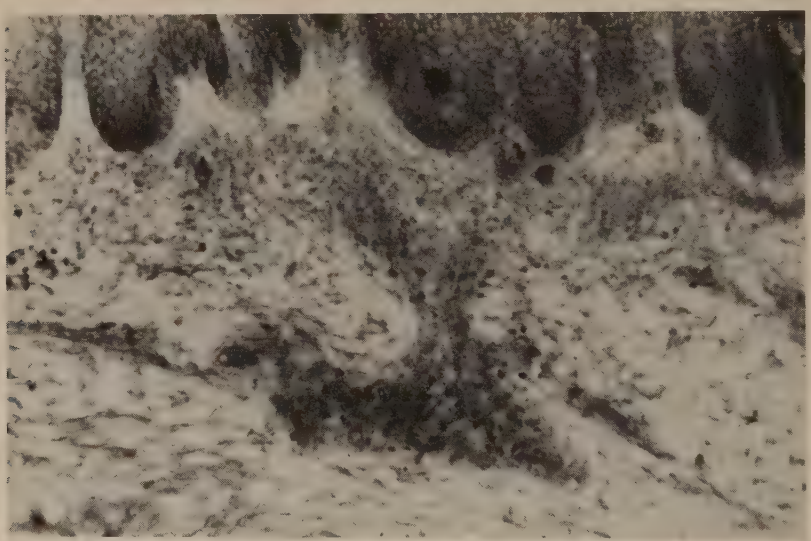

FIGURE 4. Sudan black B reaction for lipids. Lipids in epidermis, cellular infiltrate and, especially, in so-called lipophages (black dots in deep corium).

throughout its entire thickness; normally these are restricted to the transitional layer.[25]

These findings seem to indicate that in parakeratosis the rate of keratinization is so fast that apparently the unaltered physiological rate of decomposition of the lipids does not keep pace. As a result, the lipids will be present throughout the entire horny layer. An incomplete decomposition of the phospholipids in the parakeratotic horny layer accounts also for the high choline content of the psoriatic scales[112, 139] (for a summary see TABLE 3).

HISTOCHEMICAL LOCALIZATION OF PROTEINS, AMINO ACIDS, SULFHYDRYL COMPOUNDS, AND NUCLEIC ACIDS

Our present methods for the histochemical demonstration of proteins are relatively crude. For this reason one should not expect surprising results

TABLE 4

HISTOCHEMICAL LOCALIZATION OF PROTEINS, AMINO ACIDS, SULFHYDRYL, AND DISULFIDE COMPOUNDS IN NORMAL AND PSORIATIC EPIDERMIS*

Method	References	Normal skin			Psoriatic skin		Remarks
		Epidermis	Transitional zone	Horny layer	Epidermis	Parakeratotic horny layer	
Tyrosine (Millon) Tryptophane (Wieland and Bauer) Arginine (Sakaguchi)	Spier & Caneghem[140] Steigleder[148]	+	+	++	+	+++	Increased positivity in horny layer probably artefact due to dehydration
Ninhydrin and alloxan-Schiff technique (Free α-amino acid)	Steigleder[148] Braun-Falco[17]	++	++	−/+	++	+++	
$KMnO_4$-aldehyde-fuchsin reaction (keratin)	Braun-Falco & Rathjens[34]	−	−	+++	−	+++	Stains almost exclusively the membranes of the horny cells
Barrnett-Seligman-reaction							
(1) SH- groups	Moncorps[100] Sannicandro[131] Zingsheim[164] Steigleder[146] Braun-Falco[25]	++	+++	+	++	+++	
(2) SS- groups	Steigleder[148] Braun-Falco[25]	+/++	+/++	+++	+	+++	

* Literature cited refers to changes in psoriasis.

from a histochemical study of these components in the psoriatic skin, nor any clues concerning the nature of the disease (TABLE 4). At its best, the demonstration of even the simplest proteins is limited.

The horny layer stains more strongly with Millon's reagent (tyrosine) than other cutaneous structures. With Sakaguchi's technique for arginine the parakeratotic horny layer stains more strongly than the normal horny layer.[148] However, the "enrichment" of the ortho- and parakeratotic horny layer in tyrosine, tryptophan, and arginine perhaps is only apparent; it may be actually caused by dehydration.[126, 127, 140] Recently I have utilized the alloxan- and the ninhydrin-Schiff technique[161] for the demonstration of free α-amino acids.[17] With these methods, obviously, the terminal amino groups in the proteins also will be stained, while proteins linked with peptide linkage will remain unstained. The normal horny layer is weakly positive, hair keratin is negative, while the keratogenous zone often is intensely positive, as it is also toward SH- stains.[25] In psoriasis, parakeratotic horny layers show an intensive ninhydrin-Schiff positivity.[148] The enrichment of α-amino acids may be due to an accumulation of short-chain proteins, caused by the incomplete protein synthesis resulting from the precipitous keratin formation, in analogy to conditions observed in the growing hair. However, if this is the case, then the keratin in the parakeratotic horny layer of psoriatics must be considered as qualitatively abnormal, which is a hitherto unproved assumption. It is also conceivable that as a result of the rapid keratinization or of an insufficient proteolytic activity[22, 113] the amino acids and dipeptides released during keratinization are not further decomposed at an adequate rate, but remain demonstrable in the parakeratotic scales. The problem requires further study (see also Flesch and Esoda[55]).

While searching for a specific stain for keratin, Pearse found that after pretreatment with performic or peracetic acids, keratins in hair and horny layers may be visualized with Schiff's reagent.[114, 115] The same thing occurs after prolonged oxidation with acidified $KMnO_4$ solution. Aldehyde-fuchsin[66] after pretreatment with peracetic acid or acidified $KMnO_4$ is another excellent reagent for bringing out the keratinous structures of the epidermis and hair.[34, 35, 135] The mechanisms of these reactions have been discussed in detail by Braun-Falco and Rathjens.[34] With the $KMnO_4$-aldehyde-fuchsin reaction the psoriatic horny layer appears generally more weakly stained than the normal horny layer. The membranes of the cornified cells are unusually strongly outlined, as is also the case in the normal skin.[140] These findings suggest that the final consolidation of keratin occurs solely in the periphery of the cells and does not include the entire cell, possibly because of the accelerated keratinization. However, the dehydrated content of the cells is rich in substances that are needed for the keratinization or that are cast off during this process. The more strongly positive ninhydrin-Schiff reaction in the psoriatic horny layer could be similarly explained; the higher amounts of lipids, carbohydrates, and protein-bound SH- groups could be accounted for in the same way. In this connection it should be mentioned that the horny layer in psoriasis reveals a distinctly anomalous behavior in its ultraviolet absorption in the shorter wave lengths.[74]

The significance of sulfhydryl (SH-) and disulfide (SS-) groups in the skin is undisputed. It is known that these are essential for maintaining normal biological processes in the skin (keratin formation, melanogenesis, proliferation), as reviewed by Rausch and Glodny.[123]

The modern methods of Bennett[10] and Barrnett and Seligman[5, 6, 7] permit not only the visualization of the protein-bound SH-, but also, with the use of suitable controls, of SS- groups. While older histochemical methods were unable to reveal any changes in the SH- content of psoriatic skin,[41, 84] today there is no doubt that the psoriatic horny layer contains considerably more histochemically demonstrable SH- groups than the normal horny layer[25, 100, 131, 146, 163, 164] (FIGURE 5). A similarly increased SH- reaction may be observed in other physiological parakeratoses, as around the club hair, in the parakeratotic horny layer of the tongue and esophagus in the mouse and guinea pig.[50] In the normal epidermis the bandlike subcorneal, keratogenous transitional layer is especially distinctive in its affinity to SH-stains;[50, 106] it is therefore possible to look upon the parakeratotic horny layer as an extended transitional zone (TABLE 4). Such an interpretation is supported by a number of other observations.[25]

The high SH- values of psoriatic scales as reflecting an increased rate of keratinization have been confirmed by direct chemical methods.[91, 134, 163] When interpreting these findings as an expression of incomplete keratinization, two factors must be considered:

(1) Recent investigations have cast some doubt on old concepts concerning the role of the oxidation of SH- to SS- during normal epidermal keratinization.[54, 134] Spier and Caneghem also concur in this.[140] Quite similar concentrations of SS- groups have been found in the horny and Malpighian layers.[54, 134] There is also no characteristic difference between normal and psoriatic horny layers in regard to their SS- concentration (FIGURE 6). Steigleder[146, 148] found even a rather higher SS- positivity in the parakeratotic horny layer. With the Barrnett-Seligman technique the rest of the psoriatic epidermis often stains considerably weaker toward SS- than toward SH- reagents.

(2) According to Flesch the majority or all of the SH- containing components are present in the water-extractable protein fraction of the psoriatic scales and therefore have nothing to do with the keratin proper. However, one should not forget that the high SH- values in the extracts of the scales may also originate from the serum, which often contaminates the scales.

It is of decisive importance whether the histochemically demonstrable changes in the histochemical localization of the SH- and SS- groups are specific for psoriasis. According to histochemical observations, this is not the case; for example, similar reactions occur in exfoliative dermatitis as well. Conceivably this failure to differentiate between psoriasis and exfoliative dermatitis may be based on the fact that the available histochemical methods do not permit a finer quantitative analysis. Differences in the thickness of sections in the same tissue may give rise to markedly discrepant pictures.

Our increased knowledge of the biological role of nucleoproteins stimulated

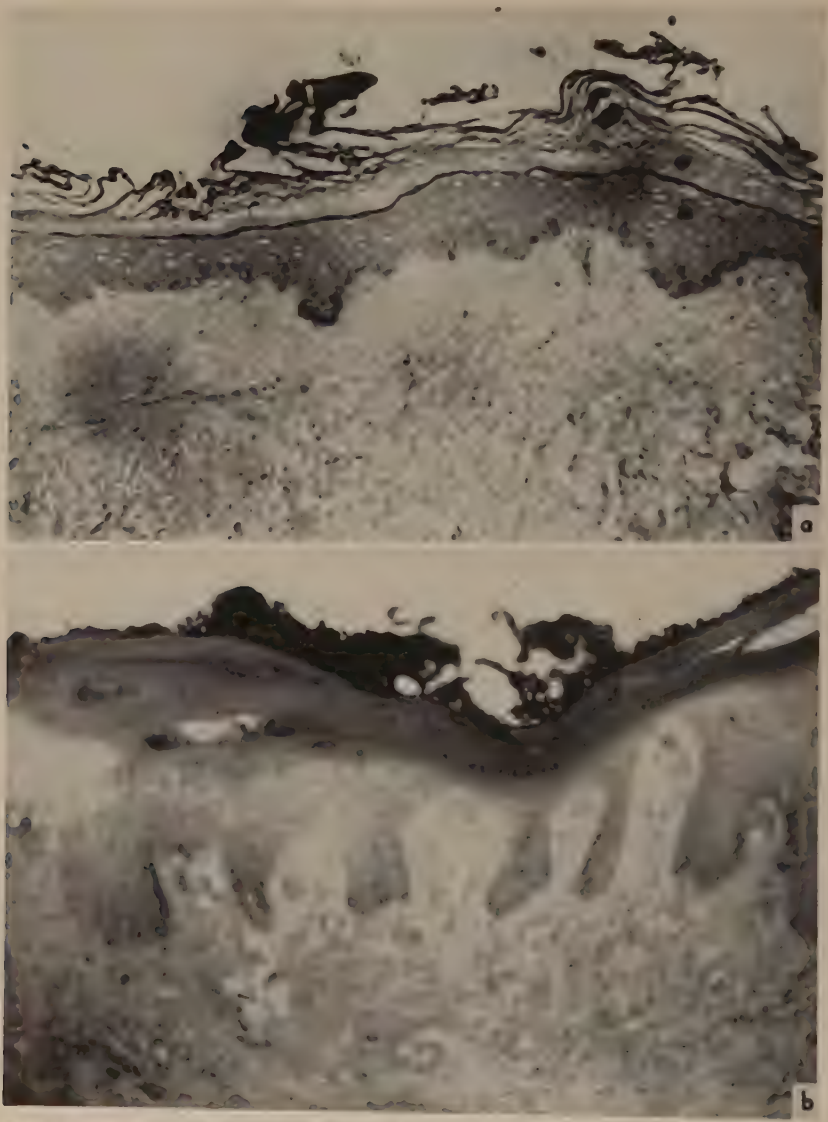

FIGURE 5. Barrnett-Seligman method for protein-bound SH- groups. (a) Normal skin, showing moderately positive reaction in the noncornified epidermal cells, intense positive reaction in the subcreneal transitional zone, and very weak reaction in the horny layer. (b) Psoriatic skin, showing moderately positive reaction in the noncornified epidermal cells and strong positivity in the parakeratotic horny layer (black masses on the surface are erythrocytes).

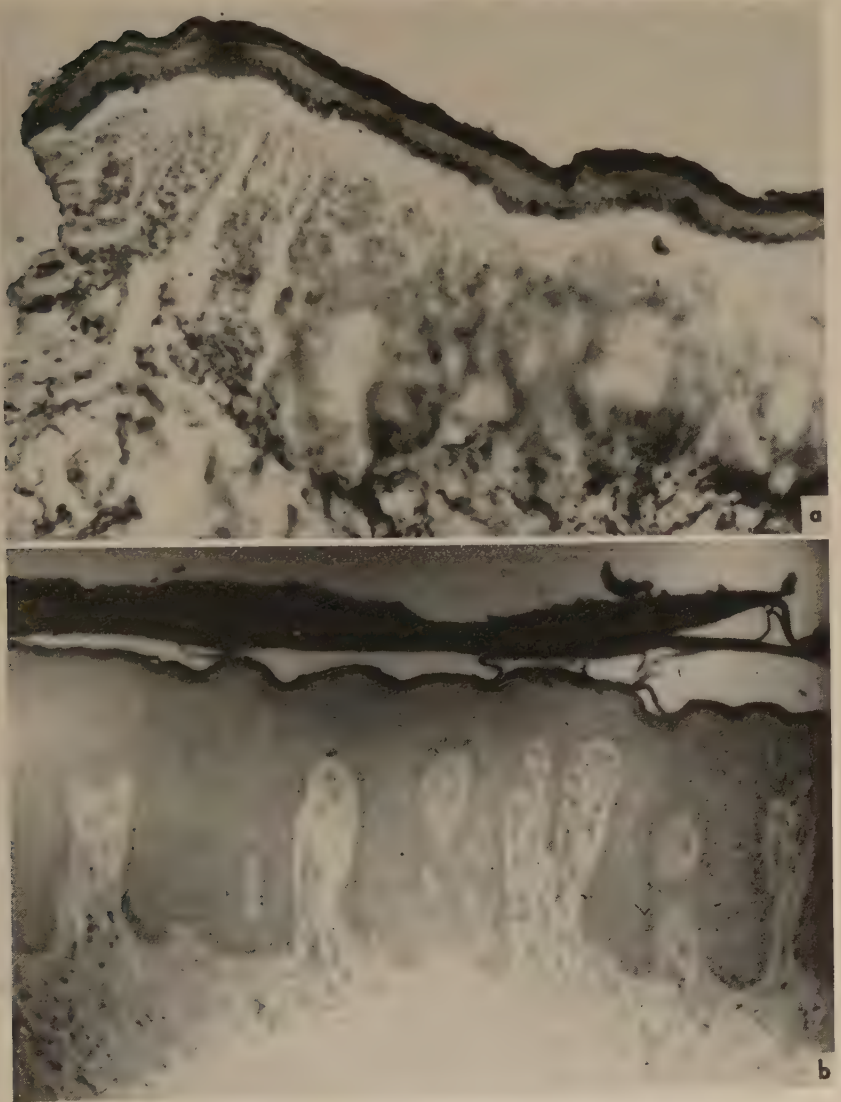

FIGURE 6. Barrnett-Seligman technique for the demonstration of protein-bound SS-groups. (a) Normal skin, showing moderately positive noncornified cells and the intensely positive horny layer. (b) Psoriatic skin, showing noncornified cells weakly or moderately positive, and the parakeratotic horny layer intensely positive.

a number of authors to conduct detailed studies on the behavior of ribonucleic acid (RNA) and desoxyribonucleic (DNA) in the normal skin and in dermatoses.

Methods for the demonstration of nucleic acids have been most critically reviewed by Sandritter.[130]

In normal skin most of the RNA is present in the cytoplasm of the basal cells; it decreases toward the stratum corneum. According to Moberger and De,[98] the stratum granulosum does not contain more RNA than the stratum spinosum. This finding disproves the theory that the granular layer contains high RNA because of the completion of keratinization in that layer.

All regenerating, multiplying, growing, secreting, or otherwise synthesizing cells have large amounts of cytoplasmic RNA that are bound to the microsomal phase. For as yet unknown reasons the cytoplasmic ribonucleoproteins are exhausted during the cytoplasmic synthesis of proteins.[3] They are replaced mostly by the RNA-depot of the nucleolus within the nucleus. Their new formation occurs much more rapidly in the nucleus than in all other cellular structures, as shown with biochemical methods. After the administration of radioactive phosphates and purines, masked RNA is found initially in the nucleus alone and only later in the cytoplasm (see Altmann's review[3]). Morphologic studies disclosed that the nucleolar substances that contain RNA are first transported to the periphery of the nucleus and are then transferred to the cytoplasm through a temporarily disrupted barrier in the membrane.[3] Accordingly, they are first found in the cytoplasm near the nucleus. Nucleoli occur primarily in cells which are engaged in intensive protein synthesis.[86] Generally their size is considered a good index of the ability of the cell to synthesize protein and RNA.[2, 85]

In the same way it is possible at present to explain the morphologic behavior of the epidermal RNA and histone-containing nucleoli in pathological conditions. The extent of the nucleolar variations, such as their number, size, and morphologic appearance, depends on the amount of nucleolar substances initially available and, consequently, on the cytoplasmic requirements for RNA for cellular activities. It is thus obvious that in the acanthotic epidermis of psoriatics the behavior of nucleoli is not specific for psoriasis, as seen in comparative studies with eczema, neurodermatitis, or mycosis fungoides.[145] In the final analysis, all these changes are merely the morphologic expressions of an altered protein synthesis brought about by functional changes (acanthosis).

For the same reasons the behavior of the cytoplasmic RNA has no value as a differential diagnostic method for the identification of various acanthotic dermatoses.[74, 145] A higher amount of cytoplasmic RNA is a general index of an increased cellular protein synthesizing ability. In the psoriatic epidermis the cytoplasmic RNA is elevated, especially in moderate acanthosis.[145] The same applies to experimentally produced acanthoses in the epidermis of animals; here, too, the cytoplasmic RNA is increased.[110] There is apparently no connection between the concentration of RNA and the type of keratinization (parakeratosis, hyperkeratosis). In the parakeratotic horny layer of psoriatics no more RNA can be demonstrated, and the nucleoli are absent in the nuclei. It may be assumed that RNA is enzymatically decomposed in the parakeratotic horny layer. In this way pentoses, bases, and phosphoric acid are released. In this respect it is of interest that the pentose content is markedly increased in the aqueous extracts of psoriatic scales.[40, 56, 67] To the best of our knowledge the behavior of the bases had

not been subjected to comprehensive study. The presence of acid valences (H_3PO_4) is suggested by the intensive orthochromasia of the psoriatic horny layer after staining with toluidine blue at *p*H 3.5 5. Another indication may be the ribonuclease-resistant pseudopositivity of the horny layer after methyl green-pyronin staining.[140] In the psoriatic scales we found elevated amounts of phosphoric acid, as compared with callus. Since these reactions in general result from a disturbed (precipitous!) type of keratinization with an incomplete degradation of cytoplasmic proteins, they are not specific for psoriasis. When carrying out biochemical studies of pentoses, bases, or phosphoric acid in the parakeratotic horny layer of psoriatics, one should keep in mind that such substances may also be liberated from the decomposing leukocytes. This may give rise to values that are not related to the disturbed keratinization.

DNA is an exclusive nuclear component. Its histochemical study has been made possible by the observation that, after mild acid hydrolysis, potential aldehyde groups of desoxyfuranose sugar are formed that react with Schiff's reagent.[53]

In the normal epidermis DNA is most concentrated in the stratum basale and the lower stratum spinosum.[70, 129, 159] The more superficial layers contain less DNA. Because of variations in the size of the nucleus, considerable errors may occur when the Feulgen reaction is used. All cells contain a definite quantity of DNA. Most of the time this amount of DNA is twice as much as the species-specific amount present in the haploid sperm cells.[117] Nevertheless, under pathological conditions fluctuations may be expected to occur in the amounts of nuclear DNA, since this substance is closely connected with growth and proliferation. In chronic dermatoses, especially in psoriasis eczema and lichen chronicus simplex, the behavior of the cell-bound epidermal DNA does not display any abnormal features that would be characteristic of the individual dermatoses.[74] Undoubtedly the apparent variations are due chiefly to fluctuations in the size of the nuclei (edema, shrinkage). As expected, the bandlike "incarcerated" nuclei of the parakeratotic horny layer give a positive Feulgen reaction as a sign of their DNA content. Very likely the persistence of nuclei in the parakeratotic horny layer is the result of a dissociation between the increased rate of keratinization and the normal rate of autoenzymatic nuclear degradation. However, there is the possibility that an enzymatic insufficiency exists, because Caneghem[140] proved that in psoriasis the activity of DNA-polymerase is inhibited. It is not known whether this process is specific for psoriasis.

Histochemical Localization of Enzymes

The main task of enzyme histochemistry is to determine the localization of enzymes in the cells and tissues. In this way one may gain information about the metabolism of the respective tissues. Unfortunately, the latter information is quite limited, because the histochemical demonstration of enzymes does not permit practically any conclusion about the actual state of metabolism. In general, in histochemical enzyme methods, high, non-physiological substrate concentrations are used that are acted upon by the

autochthonous enzymes. Therefore all studies of this nature show the potential enzymatic activity and prove that the enzymatic equipment of the tissues far surpasses the minimum required for normal metabolism. Lang,[82] for example, was able to show that the enzyme activity in the tissues is up to 600 times larger than is needed for normal activities. His observation proves that even if we induce a 99 per cent inhibition of any enzyme, we may not have any repercussions in the rate of metabolism. It also follows that in tissues where we can show with histochemical techniques a low enzymatic activity, the actual metabolism may still take place to its full extent. It is obvious, therefore, that the greatest caution is indicated when interpreting histochemical findings.[138]

The localization of cytochrome oxidase (Nadi reaction) in acanthotic dermatoses, especially in psoriasis, was subjected to detailed study by Steigleder,[143, 145] who found an increased activity of cytochrome oxidase, especially in the basal part of the rete pegs. The parakeratotic horny layer is negative.

Examination of reducing substances (and of dehydrogenase) with triphenyltetrazolium revealed a similar nonspecific distribution of reducing areas in psoriasis.[143] An increased dehydrogenase activity in psoriasis was also described by Szodoray and Sovari.[156]

These findings, however, are not specific for psoriasis; they are general indicators of an altered metabolism in the acanthotic epidermis.

Such altered metabolism is also manifested by the behavior of succinic dehydrogenase (SDH). Like other enzymes that take part in glycolysis or in the citric acid cycle, SDH, in our observations, was not demonstrable in the parakeratotic horny layer (FIGURE 7). However, Serri thought that he detected signs of SDH activity in the psoriatic horny layer.[136] In Braun-Falco and Rathjens' studies[36] the activity in psoriatic epidermis was increased, when compared with normal values.[33, 107, 136] The reaction is strongest in the basal layer of the rete pegs. Toward the surface of the epidermis the intensity continuously decreases and becomes negative at the beginning of the parakeratosis. The activity is usually preserved longer above the tips of the papillae. Our findings were confirmed by histochemical and biochemical methods.[12, 136] There is a strikingly intensive reaction in the inflammatory infiltrates underneath the epidermis.

The findings in the epidermis are not specific for psoriasis, but correspond to the extent of the acanthosis. Since there is a surprisingly good correlation between the oxygen consumption of the tissues (as measured with the Warburg technique) and the intensity of the formazan deposits,[165] one may deduce with certain reservations that the increased SDH activity in psoriasis corresponds to an increased utilization of oxygen. This would also be in accordance with Gans's experiments.[59]

The decreased SDH reaction in the eccrine sweat glands of psoriatic skin, as observed by us occasionally, could be the result of sweat retention. A positive correlation between eccrine sweat gland activity and SDH activity has also been indicated by a case of facial hemihyperhidrosis with noticeably elevated SDH activity in the tissues.[111]

FIGURE 7. Succinic dehydrogenase with the tetrazolium method. (a) Normal skin, showing moderately positive noncornified epidermis (especially in the basal layer), intensive positive reaction in the appendages, and a false positive reaction in the center of the sebaceous glands due to monoformazan dissolved in the lipids. (b) Psoriatic skin, showing the negative horny layer and subcorneal transitional zone and the strong positive acanthotic epidermis.

In the anaerobic glycolytic chain, phosphorylase catalyzes the last reversible step of glycogen synthesis, namely, the reaction: glucose-1-phosphate→ glycogen and phosphate. In the human skin it was demonstrated by Braun-Falco by histochemical means.[19] From these observations it became apparent that all noncornifying cells displayed a more or less pronounced positive reaction, indicating their ability to synthesize glycogen. Thus, the assumption that there is so-called sessile glycogen in the skin is no longer tenable. We must rather assume that the increased epidermal glycogen reflects a quite specialized metabolic situation that can be changed very rapidly.

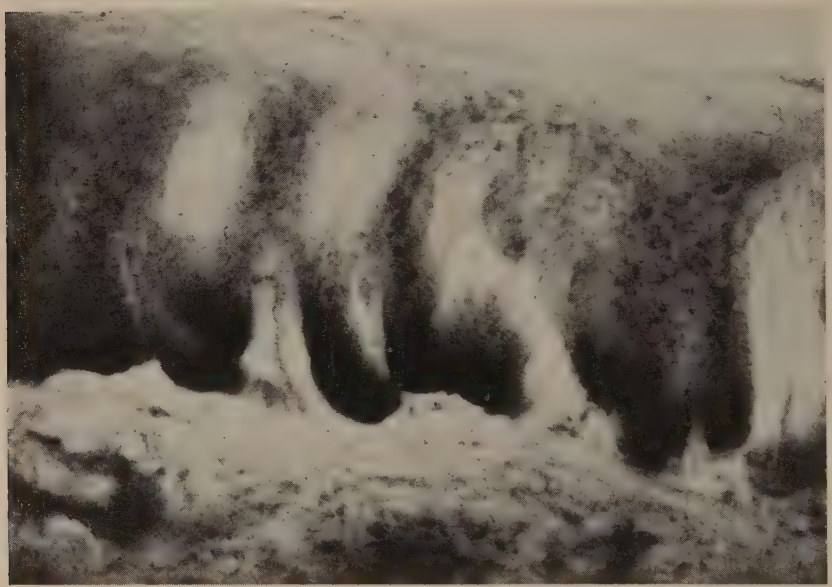

FIGURE 8. Phosphorylase with Lugol's method. Psoriatic skin, showing an intense positive reaction, especially in the tips of the rete ridges. All other noncornified epidermal cells are less positive. The horny layer is negative.

In psoriasis there is a positive reaction in all noncornified cells, but to a considerably lesser degree in the acanthotic than in the normal epidermis (FIGURE 8). A strongly positive reaction is especially marked in the endothelium of the stretched capillaries of the dermal papillae.[29]

Also, according to our observations on basal cell carcinomas, there is no connection between phosphorylase activity and the accumulation of glycogen.

Esterases

According to Gomori's classification,[64] this large group of hydrolytic enzymes may be divided into two subgroups: cholinesterases and aliesterases. In the first group, acetylcholinesterase should be separated from the other cholinesterases. The aliesterases comprise the so-called nonspecific esterases that hydrolyze the esters of short chain fatty acids (to about C4) and mono-

hydric alcohols and the lipases proper that split primarily the esters of long-chain fatty acids and glycerol. While the lipases are activated by sodium taurocholate, the nonspecific esterases are inhibited. From inhibitory studies it appears[151] that in normal and pathological skin we have all the varieties of esterases.

Cholinesterases. Although nonspecific epidermal esterases are inhibited by substances that also influence acetylcholinesterase,[151] it is by no means proved that specific acetylcholinesterase occurs in the normal epidermis. Cholinesterases in the deeper epidermal layers are probably nonspecific.[156] It has been claimed that cholinesterase is greatly decreased in the epidermis and around the papillary capillaries of the psoriatic skin.[156] The capillary dilation in psoriasis could thus be explained on the basis of a decreased decomposition of acetylcholine. According to Scott's painstaking studies,[133] nonspecific cholinesterase can be shown throughout the entire thickness of the psoriatic epidermis.

Nonspecific esterases and lipases. The indoxyl-acetate method[18] and azo-dye coupling with α-naphthyl acetate[102, 150] as substrate, give a markedly positive reaction in human epidermis. Of special interest is the intense positive bandlike reaction directly under the stratum corneum (FIGURE 9). This band of strong enzymatic activity in the keratinization zone of normal epidermis could be related to the degradation of cytoplasmic components. Studies with inhibitors reveal that the esterases in question are partly nonspecific esterases and partly lipases.[18] Apparently this latter group cannot be revealed with Gomori's Tween technique.[147]

This reaction in psoriasis is most pronounced in the rete pegs, especially in the more superficial layers, corresponding to the acanthotic proliferation. A markedly positive reaction with indoxyl acetate or with the azo-dye coupling technique occurs in the upper layers of the psoriatic epidermis. Of special interest is the striking esterase activity throughout the entire thickness of the parakeratotic horny layer, as first described by Braun-Falco.[18] Similar observations have been made with the use of the azo-dye coupling technique.[150] Inhibitory experiments have shown that there are mostly nonspecific esterases in the parakeratotic horny scales and in the subcorneal zone.[18]

The accumulation of esterases throughout the entire thickness of the psoriatic horny layer is probably related directly to the abnormally rapid process of keratinization because, in the normal skin, the elevated esterase activity is restricted to the subcorneal zone. It is the morphologic expression of the hydrolysis of fats with release of carboxylic acids which takes place in that region. In this respect it is of interest to point out the simultaneous occurrence of fats and lipids. In the normal skin, fatty acids, phospholipids, and other sudanophilic fats and esterases occur in the subcorneal transitional zone; in psoriasis, the same syntopy is extended throughout the entire parakeratotic horny layer, because the process of keratinization is too much accelerated.

In other dermatoses the parakeratotic horny layers also show esterase activity, but apparently to a lesser extent than in psoriasis.[150]

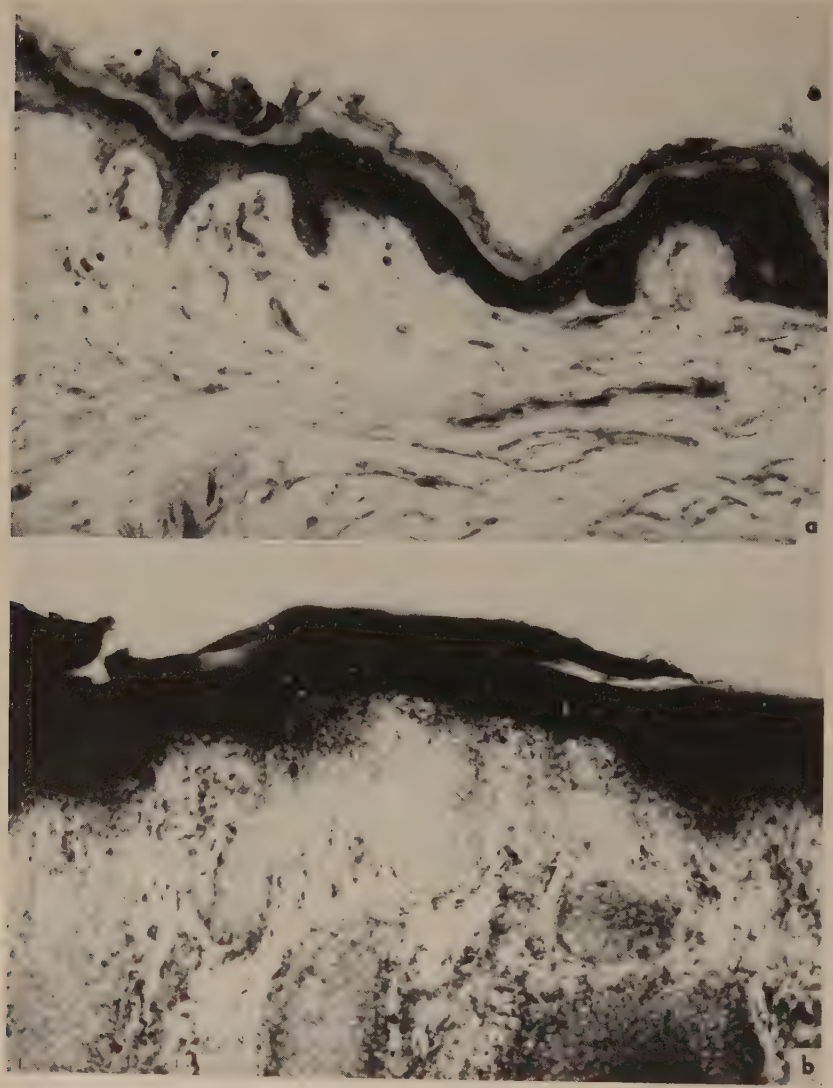

FIGURE 9. Nonspecific esterases with the azo-dye coupling method. (a) Normal skin, showing positive reaction (especially in the subcorneal transitional zone) and negative stratum corneum (with the exception of scattered positive particles on the surface). (b) Psoriatic skin, showing intense positivity in the most superficial epidermal layers and in the parakeratotic horny layer, and positive reaction in the inflammatory cells and the so-called lipophages.

Of interest is the pronounced lipase activity of the so-called "lipophages" in psoriasis,[18] and also the abnormally pronounced reactions in the eccrine sweat glands based on reactions of lipases and nonspecific esterases,[18] as shown by inhibitory studies. In all likelihood this reaction reflects the functional status of eccrine sweat glands in the psoriatic skin (sweat retention), since Steigleder and Löffler found similar relations.[150]

Phosphatases

It is almost impossible to enumerate the publications dealing with the histochemical localization of phosphatases in various tissues that have appeared since Gomori's original works.[62, 63, 65] In spite of this vast number of articles, our knowledge about the natural substrates of this group of enzymes is still very scant. Spier and Martin published an excellent review of the location and functional significance of phosphatases in human skin.[141] Most probably they play an important role in intermediate carbohydrate metabolism and in the synthesis and decomposition of nucleic acids. It is known, for example, that transphosphorylations in the presence of the adenylic acid system take place with the participation of the common alkaline phosphatase.[81] Spier and Martin[141] consider it rather surprising that alkaline phosphatase cannot be demonstrated with histochemical methods in every tissue, since the splitting of energy-rich phosphates is the immediate source of energy for all cellular functions.[81] This apparent discrepancy may be understood if we keep in mind that *in vivo* the liberation of inorganic phosphate (the phosphate shown in histochemical tests) probably represents a secondary process. The main function of the phosphatase is the regulation of the metabolic rates in interactions among labile phosphoric acid esters.[108]

Alkaline phosphatase. When carrying out the histochemical tests for alkaline phosphatase, the most striking finding is the behavior of the papillary capillaries, as will be described later (FIGURE 10). In Kopf's[79] and our studies it was found that the positive reaction in the parakeratotic horny layer[156] was nonspecific and not indicative of any enzymatic activity. However, microabscesses may be detected through the alkaline phosphatase activity of the accumulated cells.[79] As shown by investigations of normal skin (see reviews by Spier and Martin[141] and Kopf[79]), alkaline phosphatase is apparently not related in any way to the process of keratinization or to the nuclear decomposition which occurs at the same site.

Acid phosphatase. Acid phosphatase activity can be shown in all the cells of the epidermis; it is greatly increased in the transitional zone underneath the stratum corneum[95, 141] (FIGURE 11). Thus, this enzyme behaves in this zone in the same way as the reactions toward esterases and β-glucuronidase. It is reasonable to assume that the accumulation of hydrolytic enzymes in the keratogenous zone is related to the decomposition of cytoplasm and nuclei that takes place in this region. The marked accumulation of acid phosphatase reminds one of the participation of this enzyme in the physiological degradation of nuclei.[140] In the entire parakeratotic horny layer the acid phosphatase activity is markedly increased,[141] in the same way as

FIGURE 10. Alkaline phosphatase. (a) Normal skin, showing intense positive capillaries in the stratum papillare and false positive reaction in the stratum corneum. (b) Psoriatic skin, showing greatly dilated contorted capillaries in the dermal papillae and false positive reaction in the subcorneal layer.

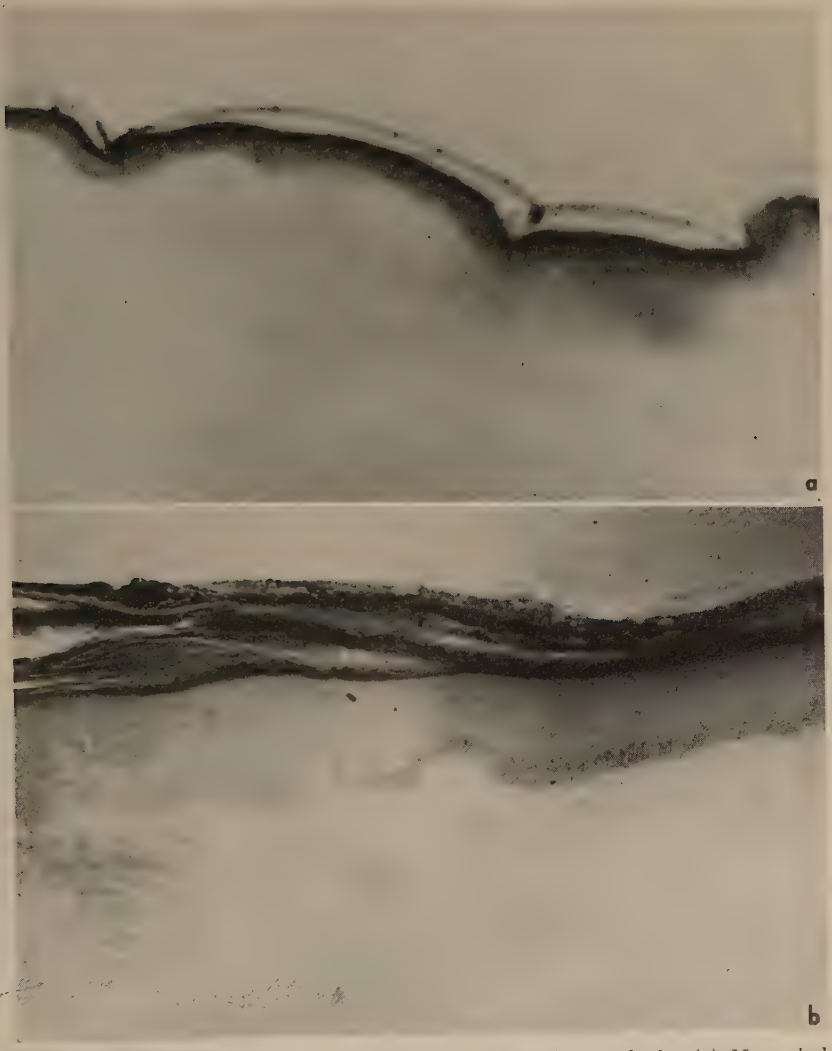

FIGURE 11. Acid phosphatase with the azo-dye coupling method. (a) Normal skin, showing a weakly positive noncornified epidermis, intensely positive reaction in the subcorneal zone, and negative horny layer. (b) Psoriatic skin, showing slight positivity in the noncornified epidermis and intensely positive parakeratotic horny layer.

the esterases[18, 150] and β-glucuronidase.[21] This acid phosphatase reaction can also be produced *in vitro* in scales of eczematous and psoriatic patients.[142] This finding shows that the behavior of acid phosphatase in the parakeratotic horny layer is not specific for psoriasis, but represents the hastened rate of keratinization which accompanies parakeratosis.

The acid phosphatase activity in the acanthotic epidermis displays no characteristic deviations from normal behavior.

In psoriatic skin β-glucuronidase can be demonstrated histochemically in all epidermal cells, corresponding to the degree of acanthotic proliferation.[21] The enzyme activity in the parakeratotic horny layer and keratogenous zone is especially striking; in normal skin only the subcorneal transitional layer reacts intensely.[20] Thus, the same localization is obtained as with esterases, acid phosphatase, SH- groups, phospholipids, and fatty acids.

Little is known about the biological function of β-glucuronidase. Although this enzyme is somehow connected with cellular proliferation, its occurrence in the zone of keratinization indicates its participation in this process. Possibly it is related to the degradation of epithelial mucins, the existence of which has been postulated time and again; these are the substances that can be shown in the parakeratotic horny layer as PAS-reactive, diastase-resistant material. For example, Meyer, Linker, and Rapport[96] have proved that β-glucuronidase can degrade to monosaccharides the disaccharides which are liberated from hyaluronic acid under the influence of hyaluronidase. It is also likely that it plays a role in steroid metabolism.

The histochemical demonstration of proteolytic enzymes is still a difficult problem. Suitable substrates (DL-alanyl-β-naphthylamide, L-leucyl-β-naphthylamide) enable us to demonstrate aminopeptidase with azo-dye coupling methods.[44] With these substrates the localization of aminopeptidase was thoroughly outlined in the normal skin, in dermatoses and tumors.[22, 24, 26] In the normal skin aminopeptidase can be demonstrated only in the border zone between epidermis and cutis. This finding is surprising, because one would expect an especially pronounced enzymatic activity in the zone of protein resynthesis, that is, in the keratogenous zone. A possible explanation may be found in the fact that the reversal of hydrolytic peptidase activity is most unlikely for thermodynamic reasons. Probably the biosynthesis of peptides from amino acids is accomplished primarily by other enzymes with the use of phosphate bond energy.[73] Even in psoriatic parakeratosis where, as we know, the rate of keratinization is increased up to three times,[140] the zone of keratinization and the parakeratotic horny layer do not contain any aminopeptidase. In psoriasis the epidermal aminopeptidase activity seems to be undoubtedly diminished when compared with normal findings.[19] This lessened activity may reflect an increased influence of an enzymatic inhibitor which is present already in the normal epidermis. The fact that in the normal skin aminopeptidase may be present in an inhibited form is shown by our observations in dermatoses with vesicles and bullae (eczema,[22] pemphigus[26]); in these conditions we could observe a "release" of the aminopeptidase activity around the blisters. In these dermatoses aminopeptidase passes into the blister fluid.[39] Wells and Babcock observed that blood serum

inhibits epithelial proteinases.[160] One could be tempted to see some connection between this and the increased capillary permeability of the much distended psoriatic capillary loops. However, there is a markedly increased aminopeptidase activity around the capillaries.

The histochemically decreased aminopeptidase activity in psoriasis could be shown by biochemical methods as well;[113] it indicates that in psoriasis the protein decomposition products are perhaps degraded to a lesser extent. Such an interpretation may also account for the marked diminution of free amino nitrogen in the psoriatic scales[55] (see TABLE 5).

The Histochemistry of the Corium in Psoriasis

Some of the histochemical aberrations in the psoriatic dermis are quite impressive; however, none of them are specific for this disease. The following regions primarily are affected: the superficial dermal zones, that is, the stratum papillare and upper stratum reticulare, with changes in the basement membrane, in the capillaries, and in the ground substance and connective tissues; the latter two are brought about by the inflammatory infiltrate. Of interest also are the changes around the eccrine sweat glands. This distribution will serve as a basis for classification.

Basement Membrane

Several authors have studied the changes of the PAS-reactive basement membrane in psoriasis.[1, 15, 74] As a rule, in psoriasis the PAS-reactive basement membrane is represented as a well-formed, slightly wavy line and displays no apparent deviation from normal skin. Wherever an extensive inflammatory infiltrate is formed, and this infiltrate reaches the dermis, the homogeneity of the PAS-reactive basement membrane disappears. In such cases we see a "skeleton" network of reticular fibers; this is intensely PAS-positive.[15] According to Braun-Falco,[17, 23] the PAS-reactive basement membrane of the human skin[154] consists of two components: (1) a network of reticular fibers; (2) a homogeneous PAS-reactive substance that probably is made of a polymerized polysaccharide complex free of proteins and lipids. Apparently the latter complex can be enzymatically degraded, leaving behind a PAS-reactive network of reticular fibers.[15, 30]

With the Hale-PAS reaction the basement membrane is also PAS-reactive. In some of our observations, however, it becomes apparently suffused by copious "liquefied," that is, depolymerized, building stones of the ground substance, and then it appears Hale-reactive in places.

These findings indicate that in psoriasis the described change in the morphologic structure of the basement membrane at the border line of the dermis and epidermis entails also physiochemical changes that may influence metabolic exchanges between epidermis and corium. The transport of metabolites toward the epidermis is greater than under normal conditions.[60]

Capillaries

It has been known for a long time that in psoriasis there is a striking dilatation of the stretched or tortuous capillaries in the elongated papillae.

TABLE 5
HISTOCHEMICAL LOCALIZATION OF ENZYMES IN NORMAL AND PSORIATIC EPIDERMIS*

Method	References	Normal skin			Psoriatic skin		Remarks
		Epidermis	Transitional zone	Horny layer	Epidermis	Parakeratotic horny layer	
Dehydrogenases	Szodoray & Sovari[156] Steigleder[143]	+	+/−	−	+++	−	
Cytochrome oxidase	Steigleder[143]	+	+/−	−	+++	−	
Succinic dehydrogenase	Braun-Falco & Rathjens[36] Serri[136]	+	+/−	−	+++	−	
Phosphorylase	Braun-Falco[29]	+++	+/−	−	++/+++	−	
Cholinesterase	Szodoray & Sovari[156] Scott[133]	+(?)	+	−	++(?)	−	
Nonspecific esterases	Braun-Falco[18] Steigleder & Löffler[150]	+	+++	−	+	+++	
Lipases	Braun-Falco[18] Steigleder & Löffler[150] Steigleder[147] Steigleder & Schultis[151]	(+)	(++)	−	(+)	(++)	Lipases can be identified only by inhibitory studies
DNA-depolymerase	Spier & Caneghem[140]					Decreased	
Acid phosphatase	Spier & Martin[141]	+	+++	−	+	+++	
Alkaline phosphatase	Szodoray & Sovari[156] Kopf[79]	−	−	−	−	−	Positive reaction in stratum corneum of psoriatics only in the region of Munro's abscesses
β-Glucuronidase	Braun-Falco[21]	+	+++	−	+	++	+++ reaction underneath parakeratosis, corresponding to the transitional zone of normal skin
Aminopeptidase	Braun-Falco[22]	+++ (only in basal layer)	−	−	(+) (only in basal layer)	−	

* Literature cited refers to psoriatic changes.

Beautiful capillary microscopic pictures showing this were published as early as 1926.[11]

Since the capillary membranes are intensely PAS-reactive and resistant to amylase, the PAS reaction is eminently suited for representing the maximally dilated capillaries in direct sections.[154] Steigleder[145] attributes diagnostic significance to such capillary changes seen with the PAS method.

Other works have clearly proved that the capillary changes do not consist solely of a simple dilatation in the stratum papillare. In this respect the high alkaline phosphatase activity of the capillaries in psoriasis is to be mentioned.[71, 77, 79, 156] In thicker sections it is apparent that at times the endothelia of the ascending, arterial limbs display a stronger enzymatic activity than do the descending capillary limbs. In our own observations in lesions of long duration the very intensely reacting capillaries frequently seemed to be elongated, while in more recent lesions they were often curled into balls.

The significance of this behavior of the capillaries in psoriasis is not clear. In conjunction with other findings, such as the discovery of alkaline phosphatase in the dermal papilla of the growing hair and in the sweat glands, it appears to be the histological expression of a high degree of metabolic activity. However, the alleged relation to the passage of metabolites through membranes and thus to vascular permeability[105] is based on speculation only.

In addition to the increased alkaline phosphatase activity, the capillaries in the elongated papillae also display a marked phosphorylase activity,[29] the interpretation of which is obscure. It may be taken as proof that in psoriasis the endothelial cells have apparently quite special metabolic activities to fulfill.

The strong aminopeptidase activity[22] in the elongated capillaries and their immediate vicinity may be interpreted in the same sense. The enzymatic activity is especially marked in the region where the papillary capillaries seem to reach the basal cells.

Ground Substance and Connective Tissue Fibers

When the skin of patients with psoriasis and psoriatic erythroderma is studied in regard to the behavior of the ground substance, one often finds in the upper dermal zones a more or less pronounced metachromasia, as a sign for the presence of acid mucopolysaccharides.[1, 15, 118, 153] They can be demonstrated also with the Hale-PAS reaction[123a] (FIGURE 12) or the Alcian blue-PAS method. The accumulation of acid, nonmetachromatic (depolymerized) mucopolysaccharides in the region of inflammatory infiltrates is especially striking. Most of the acid mucopolysaccharides stained in this way are resistant to testicular hyaluronidase. Allegra[1] is inclined to relate the increased acid mucopolysaccharide to an increased epidermal metabolism in psoriasis and believes that in this disease there is an increased production of ground substance in the dermis. This is certainly not the case. First, the fibroblasts that manufacture the ground substance are not more numerous in psoriasis. Then, the appearance of acid mucopolysaccharides certainly must be the result of an "unmixing" process. Normally the acid muco-

polysaccharides are associated with proteins and do not react metachromatically because the acid groups responsible for this reaction are blocked in their combined forms. If the mucopolysaccharide-protein combinations are split (for example, by protein degradation) the acid mucopolysaccharides become metachromatic, because they then expose the necessary free acid groups. If the acid mucopolysaccharides are later depolymerized, they lose their metachromasia and can be demonstrated only with the Hale or Alcian blue-PAS method after suitable fixation. These reactions are independent of the degree of polymerization.[31, 32] In psoriasis there is in the zone of metachromasia and inflammatory infiltrate a markedly strong aminopeptidase

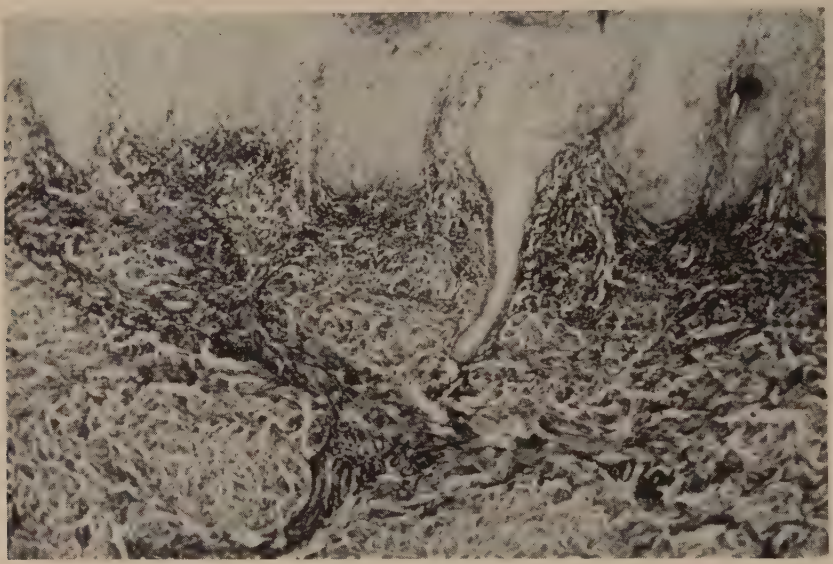

FIGURE 12. Hale-PAS reaction after treatment with diastase. Psoriatic skin, showing a dissociation of the ground substance with "acid mucopolysaccharide phanerosis" (black color) in the subepidermal zone and around the blood vessels on the left side of the picture.

reaction[22] as an indication of enhanced proteolytic activity in the dermis (the lymphocytes have a specially pronounced aminopeptidase activity). As in every other nonspecific inflammation or in the zone of invasion of epithelial cutaneous tumors,[27] through the increased proteolytic activity the combinations of acid mucopolysaccharides and proteins are dissolved. The acid mucopolysaccharides thus become visible through metachromasia ("acid mucopolysaccharide phanerosis"). The possibility exists that in their depolymerized state (negative metachromasia, positive Hale and Alcian blue-PAS reaction) the acid mucopolysaccharides may reach the intercellular spaces of the epidermis through the changed basement membrane.

These changes cannot be shown with the PAS reaction, which does not stain the acid mucopolysaccharides.[30] The intensive PAS reactivity of the reticulum fibers within the inflammatory infiltrates is striking. The other

changes in the collagenous and elastic fibers are histochemically less important and will not be discussed.

The changes around the eccrine sweat glands are quite pronounced, although they do not occur in every case. Around the terminal portions of the sweat glands there is a more or less wide zone characterized by metachromasia; more often this region is not metachromatic, but can be clearly visualized with the Hale-PAS reaction or with the Alcian blue-PAS method by its intense blue staining. The picture is that of a sweat gland edema that was also observed in the presence of epithelial tumors.[119, 122]

We believe that this is the consequence of sweat retention in psoriasis with the diffusion of sweat and its components into the surrounding connective tissue. Normally the eccrine sweat glands display a strong aminopeptidase activity.[22] Possibly these presumed "proteolytic"(?) components of sweat exude into the surrounding connective tissue and bring about a dissociation of proteins and polysaccharides as described above.

Only the application of detailed extensive work with biochemical, histochemical, and biophysical methods will lead to a real progress in our efforts to clarify the pathogenesis of psoriasis.

Summary

This review deals with the histochemical localization of inorganic substances, carbohydrates, mucopolysaccharides, lipids, protein-bound sulfhydryl, disulfide, and enzymes in the psoriatic epidermis. In the corium, the histochemical changes in the capillaries, ground substance, and eccrine sweat glands are described. Special attention is paid to the histochemistry of parakeratosis. Comparative studies with normal skin reveal far-reaching similarities between the psoriatic parakeratotic horny layer and the barrier, that is, the subcorneal transitional layer of normal skin. Both structures are characterized by marked enrichment of phospholipids, unsaturated fatty acids and lipids, amino acids or short chain polypeptides; also by increased protein-bound SH- and increased activity of hydrolyzing enzymes (nonspecific esterases, lipases, acid phosphatase, and β-glucuronidase). Enzymes participating in glycolysis and in the citric acid cycle are elevated in the acanthotic epidermis; their activity ceases when keratinization begins. The parakeratotic horny layers contain abundant amounts of PAS-positive, diastase-resistant carbohydrates that could not be more closely characterized chemically and also strongly basophilic substances that behave like acid mucopolysaccharides with respect to the Hale-PAS reaction. These substances may be related to similarly reacting intercellular material in the epidermis.

The findings in the parakeratotic horny layer indicate that from a histochemical and histoenzymatic point of view this layer corresponds to a broad transitional zone of the normal skin; the changes are probably due to an increased rate of keratinization.

The psoriatic dermis is distinguished by changes in the basement membrane, marked enzymatic activity (alkaline phosphatase, phosphorylase, and aminopeptidase), and by strongly dilated capillaries in the stratum

papillare. Changes in the ground substance with release of acid mucopolysaccharides are most pronounced in the zones of inflammatory infiltrates. They may be considered as processes of "unmixing," that is, disturbances in the normal combinations between proteins and acid mucopolysaccharides.

Many of the histochemical findings in the psoriatic epidermis and dermis are not specific for psoriasis.

Acknowledgments

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References

1. Allegra, F. 1956. Comportamento dei mucopolisaccaridi nella psoriasi. Arch. ital. dermatol. sifilog. e venereol. **28**: 36.
2. Altmann, H. W. 1952. Z. Krebsforsch. **58**: 632. *Cited in* Altmann, H. W., 1955.
3. Altmann, H. W. 1955. Zur Morphologie der Wechselwirkung von Kern und Cytoplasma. Klin. Wochschr. **33**: 306.
4. Bandmann, H. J. & H. W. Spier. 1957. Histochemische Darstellung der Plasmalreaktion an gesunder und kranker Haut. Dermatologica. **115**: 444.
5. Barrnett, R. J. 1953. The histochemical distribution of protein-bound sulfhydryl groups. J. Natl. Cancer Inst. **13**: 905.
6. Barrnett, R. J. & A. M. Seligman. 1952a. Histochemical demonstration of protein-bound sulfhydryl groups. Science. **116**: 323.
7. Barrnett, R. J. & A. M. Seligman. 1952b. Demonstration of protein-bound sulfhydryl and disulfide groups by two new histochemical methods. J. Natl. Cancer Inst. **13**: 215.
8. Belanger, L. F. 1957. The entry of Ca^{45} into the skin and other soft tissues of the rat: an autoradiographic and spodographic study. J. Histochem. Cytochem. **5**: 65.
9. Belt, W. D. & E. R. Hayes. 1956. An ultraviolet-Schiff reaction for unsaturated lipids. Stain Technol. **31**: 117.
10. Bennett, H. S. 1951. The demonstration of thiol groups in certain tissues by means of a new colored sulfhydryl reagent. Anat. Record. **110**: 231.
11. Bettmann, S. 1926. Kapillarmikroskopische Untersuchungen bei Psoriasis. Dermatol. Wochschr. **83**: 1223.
12. Binazzi, M. 1957. Ricerche sul comportamento dell' attività succinodeidrogenasica della cute. Giorn. ital. dermatol. e fasc. **5**: 509.
13. Bradfield, J. R. G. 1951. Glycogen of vertebrate epidermis. Nature. **167**: 40.
14. Braun-Falco, O. 1953. Über die Verteilung von Polysacchariden in der Epidermis bei Dermatosen, die mit Akanthose einhergehen. Dermatol. Wochschr. **128**: 1021.
15. Braun-Falco, O. 1954. Histochemische und morphologische Studien an normaler und pathologisch veränderter Haut. Arch. Dermatol. u. Syphilis. **198**: 111.
16. Braun-Falco, O. 1955. Discussion to Steigleder. 1955. Arch. Dermatol. u. Syphilis. **200**: 395.
17. Braun-Falco, O. 1955. Weitere histochemische Untersuchungen am homogenen Anteil des subepidermalen Grenzstreifens normaler menschlicher Haut. Arch. klin. u. exptl. Dermatol. **201**: 521.
18. Braun-Falco, O. 1956. Beitrag zum histochemischen Nachweis von Esterasen in normaler und psoriatischer Haut. Arch. klin. u. exptl. Dermatol. **202**: 153.
19. Braun-Falco, O. 1956. Über die Fähigkeit der menschlichen Haut zur Polysaccharidsynthese, ein Beitrag zur Histochemie der Phosphorylase. Arch. klin. u. exptl. Dermatol. **202**: 163.
20. Braun-Falco, O. 1956. Zur Histotopographie der β-Glucuronidase in normaler menschlicher Haut. Arch. klin. u. exptl. Dermatol. **203**: 61.

21. Braun-Falco, O. 1956. Histochemische Untersuchungen über das Verhalten der β-Glucuronidase-Aktivität bei Psoriasis, Basaliom und spinocellulärem Carcinom. Arch. klin. u. exptl. Dermatol. **203**: 68.
22. Braun-Falco, O. 1956. Histochemische Aminopeptidase-Darstellung in normaler Haut bei Psoriasis, Dermatitis, Basaliom, spinocellulärem Carcinom und Molluscum sebaceum. Dermatol. Wochschr. **134**: 1341.
23. Braun-Falco, O. 1957. The histochemistry of the hair follicle. Symposium on Biology of Hair Growth. London, England. Academic Press. New York, N. Y. In press.
24. Braun-Falco, O. 1957. Über die Histotopographie der Aminopeptidase bei Hauttumoren. Klin. Wochschr. **35**: 50.
25. Braun-Falco, O. 1957. Das Wesen des parakeratotischen Verhornungsmodus aus histochemischer Sicht. Klin. Wochschr. **35**: 1182.
26. Braun-Falco, O. 1957. Zur Histotopographie der Aminopeptidase bei Pemphigus vulgaris. Dermatol. Wochschr. **135**: 93.
27. Braun-Falco, O. 1957. Beitrag zum Verhalten der Grundsubstanz bei malignen epithelialen Hauttumoren. Dermatol. Wochschr. **135**: 417.
28. Braun-Falco, O. 1957. Mucophanerosis intrafollicularis et seboglandularis. Dermatol. Wochschr. **136**: 1289.
29. Braun-Falco, O. 1957. Zur Histotopographie der Phosphorylase bei Basaliom und Psoriasis. Arch. klin. u. exptl. Dermatol. **204**: 175.
30. Braun-Falco, O. 1957. Histochemie des Bindegewebes. Arch. klin. u. exptl. Dermatol. **206**: 319.
31. Braun-Falco, O. 1958. Über Untersuchungen des Hautbindegewebes mit der Hale-PAS Reaktion (Ritter & Oleson) unter normalen Bedingungen und bei Erkrankungen des Hautbindegewebes. Acta Histochem. **5**: 10.
32. Braun-Falco, O. 1958. Histochemical studies of the alterations of the ground substance in pathological conditions of the skin. 7th Brown University Symposium on the Biology of Skin; the Biology of the Dermis. Providence, R. I.
33. Braun-Falco, O. & B. Rathjens. 1954. Histochemische Darstellung der Bernsteinsäuredehydrogenase in der menschlichen Haut. Dermatol. Wochschr. **130**: 1271.
34. Braun-Falco, O. & B. Rathjens. 1954. Beitrag zum Studium histochemischer Reaktionen an Keratin und anderen cutanen Gewebsanteilen. Acta Histochem. **1**: 82.
35. Braun-Falco, O. & B. Rathjens. 1955. Die Affinität cutaner Gewebsanteile für Schiff'sches Reagens und Aldehyd-Fuchsin nach verschiedenartiger Oxydation. Hautarzt. **6**: 169.
36. Braun-Falco, O. & B. Rathjens. 1955. Über die Bernstein säuredehydrogenase-Aktivität der Haut bei Psoriasis. Arch. Dermatol. u. Syphilis. **199**: 146.
37. Braun-Falco, O. & B. Rathjens. 1956. Histochemische Darstellung von Zink in normaler menschlicher Haut. Arch. klin. u. exptl. Dermatol. **203**: 130.
38. Braun-Falco, O. & B. Rathjens. 1956. Histochemische Untersuchungen über das Verhalten von Zink in der Haut bei Psoriasis und anderen Hauterkrankungen. Dermatol. Wochschr. **134**: 837.
39. Braun-Falco, O. & K. Salfeld. 1957. Über das Verhalten der Leucin-Aminopeptidasen-Aktivität im Blutserum und Blaseninhalt. II. Untersuchungen an Patienten mit Psoriasis, Neurodermatitis diffusa, Dermatitis, Ekzem und anderen Dermatosen. Arch. klin. u. exptl. Dermatol. **205**: 103.
40. Buckup, H. & A. Szakall. 1957. Über typische Veränderungen des Gehaltes von Hornschichtextrakten an Lipoiden und Pentosen bei verschiedenen Gewerbedermatosen. Berufsdermatosen. **5**: 181.
41. Bulliard, H. & A. Giroud. 1929. Peau et Glutathion. Ann. dermatol. syphilig. **10**: 73.
42. Bullough, W. S. 1949. Epidermal mitosis in relation to sugar and phosphate. Nature. **163**: 680.
43. Burks, J. W. & H. Montgomery. 1943. Histopathologic study of psoriasis. Arch. Dermatol. and Syphilol. **48**: 479.

44. Burstone, M. S. & J. E. Folk. 1956. Histochemical demonstration of aminopeptidase. J. Histochem. **4:** 217.
45. Cormia, F. E. & V. Kuykendall. 1955. Studies in sweat retention in various dermatoses. A.M.A. Arch. Dermatol. **71:** 425.
46. Del Guasta, F. 1940. I lipidi nella pelle psoriasica. Giorn. ital. dermatol. e sifilol. **81:** 651.
47. Dogliotti, M. 1953. Über Psoriasis und Gewebslipide. Hautarzt. **4:** 17.
48. Dupré, A. 1952. Étude histochimique des glucides de la peau humaine. Thèse, Toulouse. Toulouse, France.
49. Eggleton, W. G. E. 1938. The zinc content of epidermal structures. Chinese J. Physiol. **13:** 399.
50. Eisen, A. Z., W. Montagna & H. B. Chase. 1953. Sulfhydryl groups in the skin of the mouse and guinea pig. J. Natl. Cancer Inst. **14:** 341.
51. Engman, M. F. & R. C. McCardle. 1940. A histochemical study of neurodermatitis. Arch. Dermatol. and Syphilol. **42:** 109.
52. Engman, M. F. & R. C. McCardle. 1942. A new approach to the problem of disseminated neurodermatitis. Arch. Dermatol. and Syphilol. **46:** 337.
53. Feulgen, R. & H. Rossenbeck. 1924. Mikroskopisch-chemischer Nachweis einer Nucleinsäure von Typus der Thymonukleinsäure und die darauf beruhende elektive Färbung von Zellkernen in mikroskopischen Präparaten. Z. physiol. Chem. Hoppe-Seyler's. **135:** 203.
54. Flesch, P. & A. Satanove. 1955. Sulphydryl groups and disulphide linkages in human epidermal contents. Brit. J. Dermatol. **67:** 343.
55. Flesch, P. & E. C. J. Esoda. 1957. Defective epidermal protein metabolism in psoriasis. A.M.A. Arch. Dermatol. **76:** 393.
56. Flesch, P. 1958. Personal communication.
57. Follis, R. H., Jr., H. G. Day & E. V. McCallum. 1941. Histological studies of the tissues of rats fed a diet extremely low in zinc. J. Nutrit. **22:** 223.
58. Gans, O. 1930. Zur Histo-Topochemie der gesunden und kranken Haut. Arch. Dermatol. u. Syphilis. **161:** 607.
59. Gans, O. 1952. Some observations on the pathogenesis of psoriasis. Arch. Dermatol. and Syphilol. **66:** 598.
60. Gans, O. & G. K. Steigleder. 1956. Histologie der Hautkrankheiten. 2nd ed.: 307. Springer. Berlin, Germany.
61. Gedigk, P. 1952. Histochemische Darstellung von Kohlenhydraten. Klin. Wochschr. : 1057.
62. Gomori, G. 1939. Microtechnical demonstration of phosphatase in the tissue sections. Proc. Soc. Exptl. Biol. **42:** 23.
63. Gomori, G. 1941. Distribution of acid phosphatase in the tissues under normal and under pathologic conditions. A.M.A. Arch. Pathol. **32:** 189.
64. Gomori, G. 1945. Human esterases. J. Lab. Clin. Med. **42:** 445.
65. Gomori, G. 1949. Further studies on the chemical specificity of phosphatases. Proc. Soc. Exptl. Biol. **72:** 449.
66. Gomori, G. 1950. Aldehyde-fuchsin: a new stain for elastic tissue. Am. J. Clin. Pathol. **20:** 665.
67. Grüneberg, T. & A. Szakall. 1955. Über den Gehalt an Schwefel und wasserlöslichen Bestandteilen in der verhornten Epidermis bei normaler und pathologischer Verhornung (Psoriasis). Arch. klin. u. exptl. Dermatol. **201:** 361.
68. Grütz, O. 1938. Neue histologische Beiträge zum Psoriasis-problem. Arch. Dermatol. u. Syphilis. **177:** 246.
69. Grütz, O. 1939. Die Stellung der Psoriasis im Rahmen der Lipoidosen. Verhandl. Ges. Verdgskrkh. : 81–87. *Ref. in* Zentr. Hautkrkht. **62:** 386.
70. Hardy, M. H. 1952. The histochemistry of hair follicles in the mouse. Am. J. Anat. **90:** 285.
71. Herrmann, F. 1936. Erweiterung des Verfahrens der Schnittveraschung. Differenzierung der anorganischen Struktur gesunder und kranker Haut. Z. wiss. Mikroskop. **52:** 251.

72. Hintzsche, E. 1956. Das Aschenbild tierischer Gewebe und Organe. Springer. Berlin, Germany.
73. Hoffmann-Ostenhof, O. 1954. Enzymologie. Springer. Vienna, Austria.
74. Hollander, A., S. C. Sommers & A. E. Grimwade. 1954. Histochemical and ultraviolet microscopic studies of chronic dermatoses and the corium membrane. J. Invest. Dermatol. **22**: 335.
75. von Kerckhoff, J. H. D. 1929. Beiträge zur Kenntnis der Psoriasis vulgaris. Leipzig, Germany.
76. Kernkamp, H. C. H. & E. F. Ferrin. 1953. J. Am. Vet. Med. Assoc. **123**: 217.
77. Klingmüller, G. 1958. Die Darstellung alkalischer Phosphatase in Capillaren. Hautarzt. **9**: 84.
78. Kooyman, D. J. 1935. State and localization of inorganic salts in the skin as revealed by extraction and microincineration. Arch. Dermatol. and Syphilol. **32**: 394.
79. Kopf, W. 1957. The distribution of alkaline phosphatase in normal and pathologic human skin. A.M.A. Arch. Dermatol. **75**: 1.
80. Kruse, M. 1958. Aschenbilder von normaler, psoriatischer und neurodermitischer Haut mit besonderer Berücksichtigung des Magnesiumbildes. Z. Hautkrkht. **24**: 127.
81. Lang, O. 1952. Der intermediäre Stoffwechsel. Springer. Berlin, Germany.
82. Lang, K. 1956. *Cited by* G. Siebert.[138]
83. Lansing, A. I., T. B. Rosenthal & M. H. Au. 1948. Ultrafilterable and non-ultrafilterable calcium in normal, hyperplastic epidermis and squamous cell carcinoma. Arch. Biochem. **16**: 361.
84. Lapière, M. S. 1947. Les substances à fonction sulfhydryle dans la peau normale et dans divers états pathologiques cutanés. Arch. belges dermatol. syphilol. **3**: 176.
85. Lehmann, F. E. 1952. Mikroskopische und submikroskopische Bauelemente der Zelle. 2. Coll. Deut. Ges. phys. Chem. Mosbach. 1951. Springer. Berlin, Germany.
86. Lehmann, F. E. 1956. Die submikroskopische Organisation der Zelle. Klin. Wochschr. **33**: 294.
87. Lennert, K. 1955. Die Histochemie der Fette und Lipoide. Z. wiss. Mikroskop. **62**: 368.
88. Lillie, R. D. 1954. Histopathologic Technic and Practical Histochemistry. Blakiston. New York, N. Y.
89. Lipp, W. 1954. Histochemische Methoden. Oldenbourg Verlag. Munich, Germany.
90. Lobitz, W. C., J. B. Holyoke & D. Brophy. 1955. Histochemical evidence for human eccrine sweat duct activity. A.M.A. Arch. Dermatol. **72**: 229.
91. Magnus, I. A. 1956. Observations on the thiol content of abnormal stratum corneum in psoriasis and other conditions. Brit. J. Dermatol. **68**: 243.
92. McCardle, R. C., M. F. Engman, Jr. & M. F. Engman. 1941. Spectrographic analysis of neurodermatitic lesions. Arch. Dermatol. and Syphilol. **44**: 429.
93. McManus, J. F. A. 1946. Histological demonstration of mucin after periodic acid. Nature. **158**: 202.
94. McManus, J. F. A. 1948. Histological and histochemical uses of periodic acid. Stain. Technol. **23**: 99.
95. Mescon, H., M. Gray & G. Moretti. 1954. Molluscum contagiosum: a histochemical study. J. Invest. Dermatol. **23**: 293.
96. Meyer, K., A. Linker & M. M. Rapport. 1951. The production of monosaccharides from hyaluronic acid by β-glucuronidase. J. Biol. Chem. **294**: 275.
97. Midana, A. & M. Dogliotti. 1954. Sul metabolismo dei lipidi nella cute psoriasica. Minerva dermatol. **29**: 235.
98. Moberger, G. & P. De. 1955. A cytochemical study of the cellular granules in the stratum granulosum of the epidermis. Exptl. Cell Research. **8**: 578.
99. Moberger, G. & A. Engström. 1954. Historadiographic studies on normal, hyperplastic and cancerous epidermis. J. Invest. Dermatol. **22**: 477.

100. Moncorps, C. 1929. Untersuchungen über die Pharmakologie und Pharmakodynamik von Salben und salbenincorporierten Medikamenten. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **141**: 50.
101. Montagna, W. 1955. Histology and cytochemistry of human skin. IX. The distribution of non-specific esterases. J. Biophys. Cytol. **1**: 13.
102. Montagna, W. 1956. The Structure and Function of Skin. Academic Press. New York, N. Y.
103. Montagna, W., C. R. Noback & F. G. Zak. 1948. Pigment, lipids and other substances in the glands of the external auditory meatus of man. Am. J. Anat. **83**: 409.
104. Montagna, W., H. B. Chase & J. B. Hamilton. 1951. The distribution of glycogen and lipids in human skin. J. Invest. Dermatol. **17**: 147.
105. Montagna, W., H. B. Chase & W. C. Lobitz, Jr. 1952. Histology and cytochemistry of human skin. II. The distribution of glycogen in the epidermis, hair follicles, sebaceous glands and eccrine sweat glands. Anat. Record. **114**: 231.
106. Montagna, W., A. Z. Eisen, A. H. Rademacher & H. B. Chase. 1954. Histology and cytochemistry of human skin. VI. The distribution of sulfhydryl and disulfide groups. J. Invest. Dermatol. **23**: 23.
107. Montagna, W. & V. Formisano. 1955. Histology and cytochemistry of human skin. VII. The distribution of succinic dehydrogenase activity. Anat. Record. **122**: 65.
108. Moog, F. 1946. The physiological significance of the phosphomonoesterases. Biol. Revs. **21**: 41.
109. Murtula, G. 1955. Espressioni istochimiche del dismetabolismo glucidico tissulare nei sogetti psoriasici. Minerva dermatol. **30**: 151.
110. Musha, R. 1956. Histochemical studies on experimental dermatitis. IV. Chromate and manganese dermatitis. Japan. J. Dermatol. **66**: 431.
111. Mustakallio, K. K. 1956. Succinic dehydrogenase activity of eccrine sweat glands in facial hemihyperhidrosis. Acta Dermato-Venereol. **36**: 279.
112. Ottenstein, B., N. Boncoddo, A. Walter & F. M. Thurmon. 1952. Experiments on the choline content of the skin and sebum. J. Invest. Dermatol. **19**: 105.
113. Paschoud, J. M., W. Keller & B. Schmidli. 1956. Untersuchungen über Peptidasen in der gesunden und der befallenen Haut von Psoriasiskranken. Arch. klin. u. exptl. Dermatol. **203**: 203.
114. Pearse, A. G. E. 1951. The histochemical demonstration of keratin by methods involving selective oxidation. Quart. J. Microscop. Sci. **92**: 393.
115. Pearse, A. G. E. 1954. Histochemistry. Churchill Ltd. London, England.
116. Pinkus, H. 1957. Alopecia mucinosa. A.M.A. Arch. Dermatol. **76**: 419.
117. Pollister, A. W. & H. Ris. 1947. Cold Spring Harbor Symposia Quant. Biol. **12**: 147.
118. Prieto, J. G. Jaqueti & A. P. Rodriguez. 1957. The skin mucopolysaccharides in normal and pathological circumstances, 11th Intern. Congr. Dermatol. Stockholm, Sweden. Kongressberichts. Excerpta Med. Sect. **13**.
119. Propst, A. 1956. Über das Schweissdrüsenoedem, ein Beitrag zur Pathologie des Bindegewebes. Frankfurt. Z. Pathol. **67**: 432.
120. Prunieras, M. 1957. Les espaces intercellulaires de l'épiderme. Ann. dermatol. syphilig. **84**: 538.
121. Prunieras, M. 1957. Études sur les graisses de la peau normale et pathologique. Semaine hôp. **33**: 1.
122. Randerath, E. 1948. Über Veränderungen der Schweissdrüsen in der Umgebung von Hauttumoren. Frankfurt. Z. Pathol. **59**: 30.
123. Rausch, L. & H. Glodny. 1956. Entwicklungen und Ergebnisse der Thiolforschung in dermatologischer Sicht. Zentr. Hautkrkht. **94**: 1.
123a. Ritter, H. B. & J. J. Oleson. 1950. Combined histochemical staining of acid polysaccharides and 1,2 glycol groupings in paraffin sections of rat tissues. Am. J. Pathol. **26**: 639.
124. Rivelloni, G. 1937. Distribuzione topografica delle ceneri in spodogrammi di cute umana normale. Boll. soc. ital. biol. sper. **12**: 144.

125. Rivelloni, G. 1938. Ricerche spodografiche in cute umana normale. Giorn. ital. dermatol. e sifilol. **79:** 31.
126. Rothman, S. 1954. Physiology and Biochemistry of Skin. Univ. Chicago Press. Chicago, Ill.
127. Rothman, S. 1955. Physiologische und pathologische Verhornung. Arch. Dermatol. u. Syphilis. **200:** 23.
128. Sacchi, S. 1954. Osservazioni sull' istochimica de glicogeno epidermico in alcune dermatosi. Riv. istochim. norm. e patol. **1:** 61.
129. Sandritter, W. 1953. Ultraviolettmikrospektrophotometrische Untersuchungen an Plattenepithel. Frankfurt. Z. Pathol. **64:** 520.
130. Sandritter, W. 1955. Die Nachweismethoden der Nucleinsäuren. Z. wiss. Mikroskop. **62:** 283.
131. Sannicandro, G. 1932. La reazione nitroprussica nello studio della cheratinizzazione epidermica. Arch. ital. dermatol. sifilog. e venerol. **8:** 647.
132. Sasakawa, M. 1921. Beiträge zur Glycogenverteilung in der Haut unter normalen und pathologischen Zuständen. Arch. Dermatol. u. Syphilis. **134:** 418.
133. Scott, A. 1958. Distribution and behaviour of cutaneous nerves. Brit. J. Dermatol. **70:** 1.
134. Van Scott, E. J. & P. Flesch. 1954. Sulfhydryl groups and disulfide linkages in normal and pathological keratinization. Arch. Dermatol. and Syphilol. **70:** 141.
135. Scott, H. R. 1953. Demonstration of keratin with aldehydefuchsin. Nature. **172:** 674.
136. Serri, F. 1955. La succinodeidrasi nella cute umana normale e patologica. Minerva dermatol. (Suppl. 12.) **30**(4).
137. Shelley, W. B. & H. Mescon. 1952. Histochemical demonstration of secretory activity in human eccrine sweat glands. J. Invest. Dermatol. **18:** 289.
138. Siebert, G. 1956. Biochemie der Enzyme. Acta Histochem. **2:** 122.
139. Snider, B. L., H. R. Gottschalk & S. Rothman. 1949. The fate of choline in normal and pathologic keratinization of the epidermis. J. Invest. Dermatol. **13:** 323.
140. Spier, H. W. & P. von Caneghem. 1957. Zur Histochemie der Verhornung. Arch. klin. u. exptl. Dermatol. **206:** 344.
141. Spier, H. W. & K. Martin. 1956. Histochemische Untersuchungen über die Phosphomonoesterasen der gesunden Haut mit Hinweis auf Befunde bei Hauterkrankungen. Arch. klin. u. exptl. Dermatol. **202:** 120.
142. Spier, H. W., G. Pascher & K. Martin. 1955. Phosphomonoesterasen an der Hautoberfläche. Dermatologica. **111:** 9.
143. Steigleder, G. K. 1952. Histochemische Untersuchungen im psoriatischen Herd über Oxydation, Reduktion und Lipoidstoffwechsel. Arch. Dermatol. u. Syphilis. **194:** 296.
144. Steigleder, G. K. 1954. Zur Histochemie und Histologie der Psoriasis- und Neurodermitispapel. Vortr. Ver. Südwestdtsch. Dermatol., Apr. 1953, Marburg. Dermatol. Wochschr. **129:** 79.
145. Steigleder, G. K. 1955. Zur Funktion der Acanthose. Arch. Dermatol. u. Syphilis. **200:** 377.
146. Steigleder, G. K. 1956. Zum Histochemischen Nachweis SH- und SS-Gruppenhaltiger Substanzen in der normalen und pathologisch veränderten Haut des Menschen. Klin. Wochschr. **34:** 495.
147. Steigleder, G. K. 1956. Zum histochemischen Nachweis von Lipase in der normalen Haut und Leber der Ratte und der normalen und pathologisch veränderten Haut des Menschen. Z. Hautkrkht. **20:** 270.
148. Steigleder, G. K. 1957. Die Histochemie der Epidermis und ihre Anhangsgebilde. Arch. klin. u. exptl. Dermatol. **206:** 276.
149. Steigleder, G. K. 1957. A critical analysis of the parakeratotic horn layer. 11th Intern. Congr. Dermatol. Stockholm, Sweden. 1957. Kongressberichts. Excerpta Med. Sect. **13:** 81.
150. Steigleder, G. K. & H. Löffler. 1956. Zum histochemischen Nachweis unspezifischer Esterasen und Lipasen. Arch. klin. u. exptl. Dermatol. **203:** 41.

151. Steigleder, G. K. & K. Schultis. 1957. Zur Histochemie der Esterasen der Haut. Arch. klin. u. exptl. Dermatol. **205**: 196.
152. Steiner, K. 1955. A histochemical study of epidermal glycogen in skin diseases. J. Invest. Dermatol. **24**: 599.
153. Steiner, K. 1957. Mucoid substances and cutaneous connective tissue in dermatoses. III. Cutaneous mucopolysaccharides in inflammation of the skin. J. Invest. Dermatol. **28**: 419.
154. Stoughton, R. & G. Wells. 1950. A histochemical study on mucopolysaccharides in normal and diseased skin. J. Invest. Dermatol. **14**: 37.
155. Suskind, R. R. 1954. Eccrine function in psoriasis. J. Invest. Dermatol. **23**: 345.
156. Szodoray, L. & E. Sovari. 1953. Untersuchungen der Gewebe-Enzyme der Haut bei Schuppenflechte. Acta Morphol. Acad. Sci. Hung. **3**: 111.
157. Unna, P. G. 1913. Biochemie der Haut. Fischer. Jena, Germany.
158. Unna, P. G. 1925. Lebensvorgänge in der Haut des Menschen und der Tiere; für Ärzte, Tierärzte, Biologen und naturwissenschaftlich Interessierte. Deuticke. Leipzig, Germany.
159. Washburn, W. W. & T. E. Blocker, Jr. 1954. The histochemistry of burned human skin. I. Glycogen, ribonucleic acid and desoxyribonucleic acid. Plastic & Reconstruction Surg. **14**: 393.
160. Wells, G. C. & C. Babcock. 1953. Epidermal protease. J. Invest. Dermatol. **21**: 459.
161. Yasuma, A. & T. Ichikawa. 1953. Ninhydrin-Schiff and alloxan-Schiff staining. J. Lab. Clin Med. **41**: 296.
162. Yuyuma, H. 1935. Über die histologische Untersuchung der Glycogenverteilung in der leprösen Haut. Mit besonderer Berücksichtigung der Beziehung zwischen der Funktion der Schweissdrüsen und der Schwankung des Glycogens. Japan. J. Dermatol. **37**: 811. *Ref. in* Zentr. Hautkrkht. **52**: 377 (1936).
163. Zingsheim, M. 1952. Die Rolle freier Sulfhydrylgruppen bei der Schuppenflechte. Deut. med. Wochschr. **77**: 1630.
164. Zingsheim, M. 1954. 1-(4-Chlormercuriphenylazo)-Naphthol-2 zur Darstellung der Sulfhydrylgruppen bei Psoriasis. Z. Hautkrkht. **17**: 71.
165. Zweifach, B. W., M. M. Black & E. Shorr. 1950. Proc. Soc. Exptl. Biol. Med. **74**: 848.

APPLICATION OF PAPER ELECTROPHORESIS TO THE DIAGNOSIS OF PSORIASIS: A STUDY OF PSORIATIC SCALE EXTRACTS*

By Daphne Anderson Roe

Department of Physiology, Vassar College, Poughkeepsie, N. Y.

Introduction

One hundred and fifty years ago Robert Willan[1] adopted the name psoriasis to define a disease entity characterized by the appearance of scales on the skin surface.

These scales are the subject of the present investigation, because it is believed that a study of their composition will lead, not only to a method for the diagnosis of psoriasis, but also to a better understanding of the pathogenesis of the disease.

It has been amply demonstrated by Flesch and Esoda,[2] by Grüneberg and Szakall,[3] and by Braun-Falco[4] that the epidermal defects in psoriasis involve anomalies of the water-soluble components of the horny layers. Among the anomalous components, the greatly increased soluble proteins are of special interest. In an effort to clarify the biochemical basis for these defects, the following experiments have been carried out on the proteins extracted from scales of four patients with psoriasis.

Methods for Extraction of the Psoriatic Scales

Psoriasis scales were washed with ether, dried, and homogenized in a Waring Blendor with a borate buffer† at *p*H 9.4 for 15 minutes. Ten-gram samples of scales were used with 100 ml. of the buffer. Following this homogenization, the contents of the Waring Blendor were transferred to a flask; a further 100 ml. of the buffer was added to remove scale particles adhering to the sides of the Blendor. The scales were then extracted in the flask for 48 hours in the icebox at 6° C. The extract was filtered and dialyzed for 24 hours against the borate buffer at 6° C. The filtrate was concentrated to approximately half its original volume by evaporation in a dialyzing sac, in a current of warm air.

Isolation of the Proteins in the Psoriatic Extract

(1) The proteins in the filtrate were isolated by fractionated precipitation with ammonium sulfate.[5] With this method, 3 proteins precipitated maximally at 30, 60, and 80 per cent saturation of the salt. These proteins were named A, B, and C, respectively (FIGURE 1). After precipitation, each

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† Borate buffer: solution A, KCl 1.49 gm., H_3BO_3 1.23 gm., distilled water to 100 ml.; solution B, 0.2 M NaOH; add 50 ml. A to 32 ml. B and dilute to 200 ml. with distilled water.

protein was dialyzed against distilled water and re-precipitated at its isoelectric (isoionic) point.

(2) The concentrated filtrate was applied to Whatman No. 1 paper strips and electrophoresis was carried out by the horizontal open-strip method, either for 4 hours at 270 v. E.M.F. or for 18 hours at 120 v. E.M.F. in an Arthur H. Thomas apparatus. The apparatus was filled with a borate buffer solution identical in composition with that used for the extraction of the psoriatic scales. The paper strips were then dried at 70° C. for 10 minutes and stained with bromphenol blue.[6] Three proteins could then be identified on the paper (FIGURE 2).

(3) Proteins A, B, and C were each dissolved separately in the borate buffer and subjected to paper electrophoresis for the same periods and at the

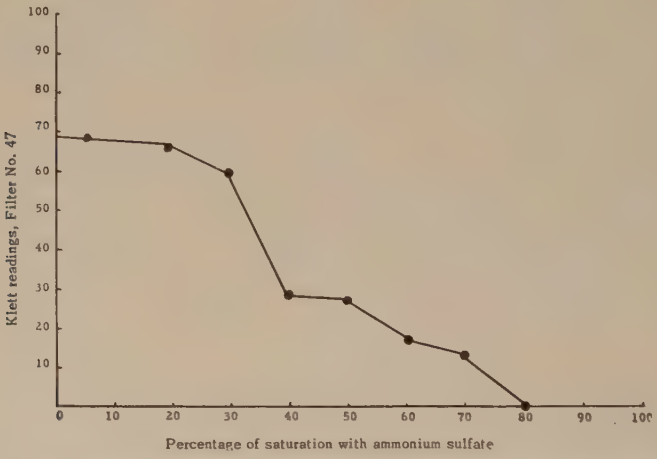

FIGURE 1. Turbidity measurements in extract of psoriatic scales with increasing concentrations of ammonium sulfate.[5] Note 3 peaks corresponding to 3 protein fractions.

same voltages used with the concentrated filtrate. By this method it was possible to identify the position of each of these proteins on the paper strips.

Identification of Proteins A, B, and C

Protein A. This protein precipitated maximally from aqueous solution at *p*H 5.5, and this has been taken as the isoelectric point of the protein. The precipitate is fibrous in character (FIGURE 3). When these fibers were dried in extension, they exhibited marked birefringence (FIGURE 4). Electron micrographs of the protein* revealed fibrils approximately 65° Å diameter, which tended to aggregate laterally to form bundles 200 Å diameter (FIGURE 5). These characteristics are identical with those of the protein

* The protein was centrifuged to form pellets approximately 2 mm. in diameter. The pellets were fixed in 2 per cent osmic acid in 0.44 M sucrose and dehydrated in methyl alcohols containing 1 per cent phosphotungstic acid. They were then embedded in a methacrylate resin and sectioned for electron microscopy. Studies of this material were made by C. C. Selby.

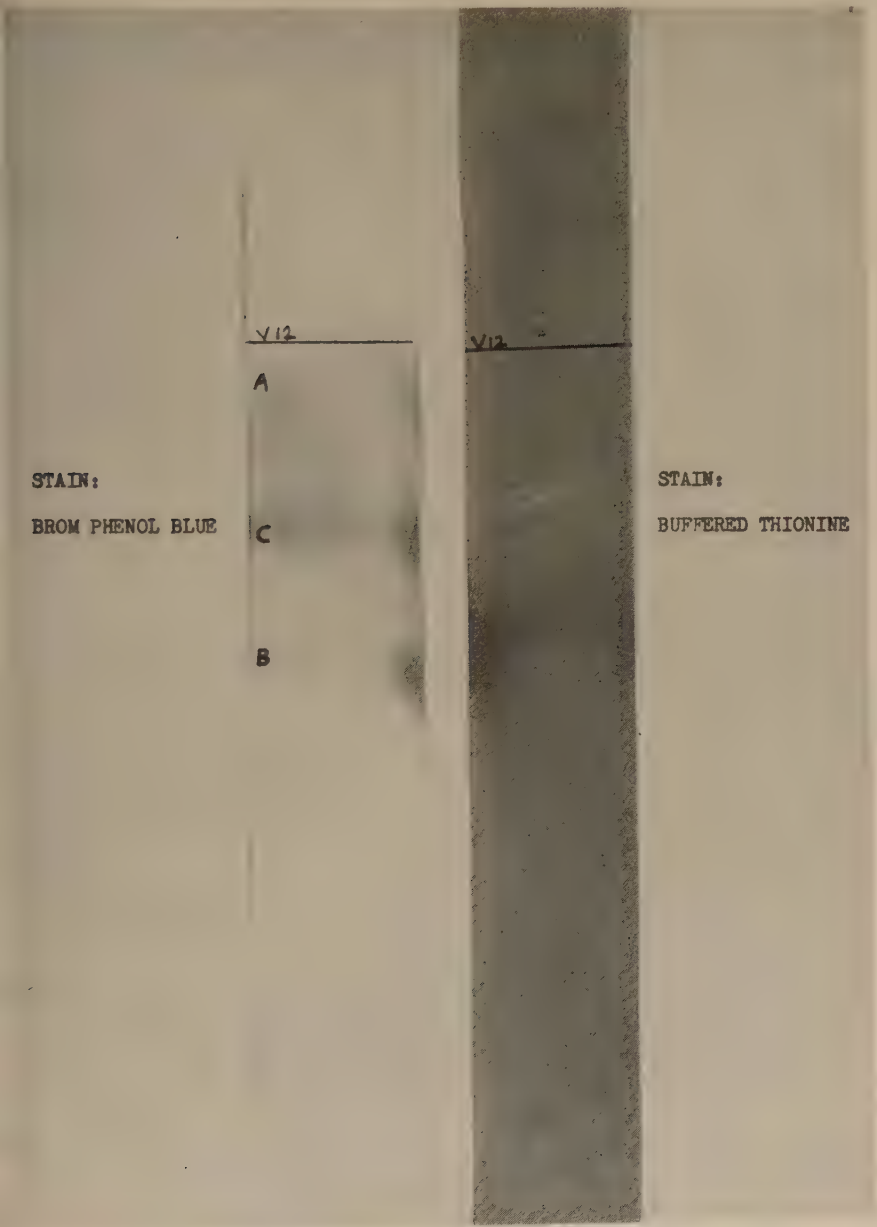

FIGURE 2. Paper strips showing proteins A, B, and C stained with bromphenol blue and the identification of protein B by its metachromatic staining with buffered thionin. Electrophoretic separation of psoriatic extract on these paper strips was run for 4 hours at 270 volt E.M.F.

tonofibrin,[7] which has previously been extracted from normal cellular epidermis. Tonofibrin is believed to be a keratin precursor, which forms the tonofibrils. Sulfhydryl groups were not present in this protein.[8]

Protein B. This is a globular protein with an isoelectric point of 4.2. It precipitates first as a fine flocculent substance and on concentration by centrifugation; it takes on a gelatinous appearance. On drying and exposure to air, it darkens to a brown-black color. It is not precipitated by heat. Qualitative analysis revealed the presence of sulfhydryl groups.[8] When

FIGURE 3. Fibers of protein A dried on a silicone-coated glass slide. ×150.

this protein was subjected to paper electrophoresis and the paper strips were subsequently stained with a buffered thionin solution at *p*H 4.0,* the protein band exhibited striking metachromasia (FIGURE 6). This metachromasia was destroyed by incubation of the paper strips with testicular hyaluronidase or malt diastase.† The application of the periodic acid-Schiff staining

* The paper strips were stained for 30 minutes in 0.05 per cent thionin in an 0.01 M acetate buffer at *p*H 4.0. The excessive dye was removed by washing with the acetate buffer.

† The papers were immersed (1) in a solution containing 2 mg. of testicular hyaluronidase in a phosphate buffer at *p*H 6.47 for 1 hour at 37° C.; (2) in a solution of malt diastase 1:1000 in the same phosphate buffer for 1 hour at 37° C. In each case, the papers were washed after incubation and stained with buffered thionin.

FIGURE 4. Fibers of protein A prepared as in FIGURE 3 and viewed under polarized light. ×150.

FIGURE 5. Electron micrographs of sectioned protein pellets fixed in 2 per cent osmic acid. Left, tonofibrin extracted from normal cellular epidermis. Right, fibrous protein A extracted from psoriatic scales. ×76,000.

method to the strips[9] resulted in a faint violet-red band, and a reddish-brown band was obtained when the strips were treated with diphenylamine and formaldehyde.[10] These tests indicate that protein B is a glycoprotein. This was confirmed by estimation of the carbohydrate content of the protein

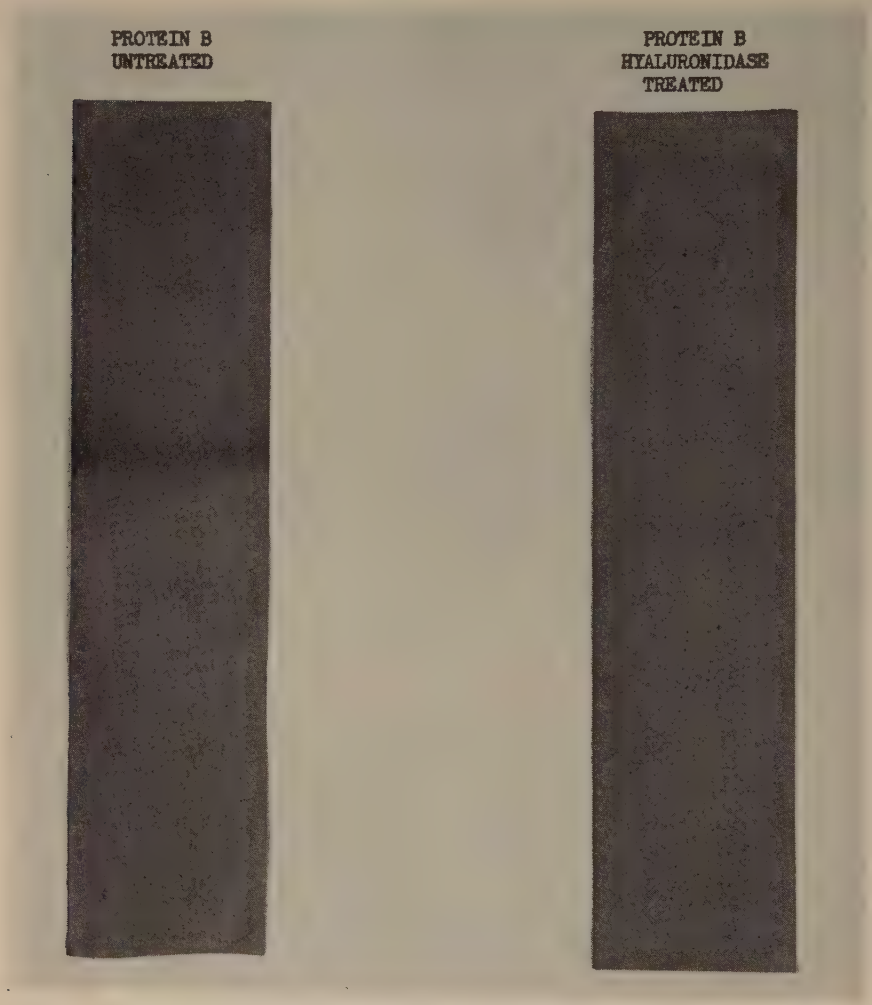

FIGURE 6. Paper strips after electrophotoretic run of protein B for 4 hours at 270 volt E.M.F. Left, untreated paper stained with buffered thionin. Right, paper strip treated with testicular hyaluronidase and then stained with buffered thionin.

by the orcinol method[11] when 4.5 mg. per cent hexose was found to be present.

When partial hydrolyzates of the protein—obtained by dissolving B in 0.1 N NaOH and heating it for 1 hour—were subjected to paper electro-

phoresis, *N*-acetylglucosamine could be identified by the acetylacetone-dimethylaminobenzaldehyde reagents[12] and by ninhydrin in *n*-butanol.[13] The presence of sulfate in the hydrolyzate was also indicated on spot tests by the use of barium chloride and sodium rhodizonate.[14]

When the protein was further hydrolyzed with 2 N H_2SO_4 for 30 minutes at 100° C. and the hydrolyzate was neutralized with solid barium carbonate, the presence of hexose could be revealed by the aniline phthalate reagent.[15]

These qualitative tests give some information as to the composition of the carbohydrate radical of protein B, suggesting that it may be a chondroitin sulfate.

Protein C. This protein can be precipitated from very acid solutions, the precipitate coming down first as a coarsely flocculent material and then, as the isoelectric point is approached (*p*H 3.4), as long threads. The protein gave a positive Feulgen reaction in spot tests as well as on paper strips. After partial hydrolysis (with N NaOH at 70° C. for 1 hour) nucleotides were identified by the molybdic acid reagent.[16] Further hydrolysis, as carried out with protein B, released pentoses that could be demonstrated by the aniline phthalate method.[15] These properties indicate that protein C is a nucleoprotein.

Sources of the Proteins in the Psoriatic Scale Extracts

We can summarize the results of the investigations described above by stating that the extracts of psoriatic scale contain a fibrous protein, probably a keratin precursor, a glycoprotein containing a sulfated mucopolysaccharide, and a nucleoprotein. The sources of these proteins have been elucidated by histological studies of psoriatic scales.

The origin of the fibrous protein has not yet been fully investigated. Preliminary studies of unstained thin sections of psoriatic scales before extraction have revealed the presence, in the parakeratotic cells, of birefringent fibrous structures with their long axes oriented in some areas parallel to the surface and in others perpendicular to it. This birefringence disappears after extraction with the borate buffer. Furthermore, the similarity of this protein to tonofibrin suggests that it may be the keratin precursor forming the tonofibrils. We can postulate that in psoriasis, where keratinization is incomplete, tonofibrin persists and is not converted into mature keratin.

For the demonstration of protein B, paraffin sections of psoriatic scales were stained with buffered thionin before and after incubating the sections with testicular hyaluronidase[17] and after extracting the scales with borate buffer for 30 minutes (FIGURE 7, see FRONTISPIECE). Metachromatic material can be seen in the untreated sections, and it appears that this material is localized in the intercellular spaces and within the cytoplasm of the parakeratotic cells. Testicular hyaluronidase destroys the metachromasia; the borate buffer removes the metachromatic material from the psoriatic cells.

Lison[18] stated that metachromasia appears to be the property of those polysaccharides or their salts that are sulfuric acid esters, for example, chondroitin sulfate or mucoitin sulfate.

Hale,[19] commenting on this statement, adds that metachromasia is dependent on the presence of the $-OSO_3H$ radical, since addition or removal of this radical produced or destroyed metachromasia.

Thus, from the results of the studies already made, it can be seen that protein B incorporates a sulfur-containing polysaccharide having the properties of chondroitin sulfate.

The source of protein B has been shown by histochemical means; its significance will be discussed in a later section of this paper.

We may presume that protein C is extracted from the nucleus or nuclear remnants of the parakeratotic cell. Thus far, however, no investigations have been made to prove this hypothesis.

Comparative Studies

In order to discover whether these findings were specific for psoriasis, comparative studies were performed with callus, normal epidermis, and scales from two cases of nonpsoriatic exfoliative dermatitis (a case of ichthyosiform erythroderma and a case of pityriasis rubra of unknown etiology). These samples were extracted by the same method used for the psoriatic scales. The epidermis was separated and prepared for extraction by a method I have described elsewhere.[20]

The filtered and dialyzed extracts from these sources were concentrated by evaporation in a dialyzing sac and then subjected to paper electrophoresis. The paper strips were afterward dried and stained (1) with bromphenol blue and (2) with buffered thionin. The results of these experiments are summarized in TABLE 1.

TABLE 1
SUMMARY OF COMPARATIVE STUDIES BY MEANS OF PAPER ELECTROPHORESIS

Extract	Bromphenol blue	Buffered thionin
	No. of protein bands	Metachromasia
1. Callus	1 (Faint 2nd band)	−
2. Normal epidermis	3	+−
3. Exfoliative dermatitis	2	++
4. Psoriasis	3	++

By comparing these paper strips with those obtained from psoriatic extracts, it was found that callus does not contain protein A, B, or C, but that these proteins were present in normal epidermis. However, in the epidermal extracts, protein B is apparently present only in very small amounts, as evidenced by a faint band in that position on the paper strips, which showed barely discernible metachromasia. The extracts from the two cases of nonpsoriatic exfoliative dermatitis both showed two bands, one in the position of protein B and the other in the position of the major protein

component extracted from callus.* The band in the position of protein B showed intense metachromasia. There was no evidence of the presence of protein A or C in these extracts.

Furthermore, when fractionated precipitation was carried out on the extracts from exfoliative dermatitis, neither the fibrous protein A nor the nucleoprotein C could be isolated.

Equal weights of scales from case 4 of psoriasis and from case 2 of exfoliative dermatitis (pityriasis rubra) were extracted with distilled water at 70° C. for 1 hour. The extracts were then filtered and the salt concentration was brought to about 0.5 per cent with a few milliliters of saturated sodium acetate. Three volumes of ethanol were added to each filtrate, whereupon a mucoid substance precipitated. The precipitates were washed with ethanol and dissolved in distilled water to give clear viscous solutions. These solutions were subjected to paper electrophoresis; when the strips were subsequently stained with buffered thionin, a metachromatic band was revealed.

Portions of the viscous solution were also partially hydrolyzed with 0.1 N NaOH at 70° C. for 1 hour and again applied to the paper strips for electrophoresis. These strips were treated (1) with acetylacetone-dimethylaminobenzaldehyde reagents and (2) with ninhydrin in *n*-butanol. In each case *N*-acetylglucosamine was identified. This method was used by Partridge[22] for the isolation and identification of chondroitin sulfate from cartilage. The positive reactions suggest that chondroitin sulfate is present in both these extracts.

A simple histological study was made of the scales of the nonpsoriatic exfoliative dermatitis by staining material with buffered thionin. This showed that metachromatic material was present, but that it was entirely extracellular in distribution.

These studies show that the presence of glycoprotein is not specific for psoriasis; from the limited material now available, it appears that intracellular glycoprotein is present in psoriasis only. Furthermore, the simultaneous occurrence of the fibrous protein with the glycoprotein is apparently characteristic for psoriatic scales. It must be emphasized that these comparative studies are of a preliminary nature; it would be premature to make a definitive statement in this regard.

Diagnosis of Psoriasis by Paper Electrophoresis

Paper electrophoresis gives a convenient and simple method for the separation of the proteins in the psoriatic extract. By staining the dried paper strips with bromphenol blue and with buffered thionin, the presence of the characteristic proteins may be demonstrated. This method could be used as a diagnostic procedure in many clinical laboratories and dermatological departments. Whether this test could be used as a prognostic tool or to

* In the borate buffer extracts of callus there are apparently two proteins, although one of these is present only in very small amounts. On the paper strips neither of these proteins corresponds in position to protein A, B, or C. We may suppose that these proteins are keratins A and B, described by Matoltsy and Balsamo,[21] keratin A being the only significant protein dissolved in the buffer at *p*H 9.4.

follow treatment in psoriasis remains a subject for further investigation. As yet we have not determined whether the amount of glycoprotein or fibrous protein present varies with severity of the disease and whether under therapy, the glycoprotein is removed.

Discussion

The present work may give a clue to the pathogenesis of psoriasis. It has been suggested that mucopolysaccharides may be essential to the formation of collagen fibers;[23] they may also be essential to the formation of the prekeratins. Birbeck and Mercer[24] have shown that in hair formation the cortical prekeratin fibrils aggregate within a sulfur-containing matrix.

Whether this matrix contains mucoproteins has not been demonstrated. However, Montagna[25] has shown that the outer sheath of the growing hair follicle contains mucopolysaccharide.

Montagna has also shown that in the normal epidermis the entire stratum Malpighii stains metachromatically. The epidermis contains substances, reactive to the periodic acid-Schiff staining technique, which are located in the stratum granulosum, in the nodes of Bizzozero, and in the intercellular spaces between the intercellular bridges. These are presumably mucopolysaccharide-containing materials and probably are glycoproteins. Therefore, Montagna[25] has suggested that mucopolysaccharides bear some relationship to the process of keratinization.

We know from our studies that during the process of keratinization the glycoprotein disappears and that, in the horny layer, it is no longer to be found. In psoriasis, the presence of the intracellular glycoprotein in the parakeratotic scales may in itself inhibit the maturation of the keratin. The reason for the persistence of the glycoprotein is not known. It may represent a reversion to a more primitive type of epidermal differentiation, as found in invertebrates and the more primitive vertebrate phyla[26-30] or, more probably, a failure of an enzyme system whereby the glycoprotein is normally hydrolyzed. However, as yet, we have no experimental evidence to substantiate either of these theories.

Finally, these investigations may lead us to a better understanding of the relationship of psoriasis and psoriasis arthropathica. A comparison of the glycoproteins in the synovial fluids and in the psoriatic scales may give a biochemical basis for the interrelationship of these two manifestations of the disease.

Summary

Psoriatic scales have been extracted with a borate buffer at *p*H 9.4 and 3 proteins isolated, by fractionated precipitation, from the filtered extracts. These proteins have also been separated and identified by paper electrophoresis, followed by selective staining of the paper strips. In this way, it has been shown that fibrous protein, glycoprotein, and nucleoprotein are present in the extracts. The fibrous protein is similar to or identical with tonofibrin, which has previously been extracted from normal epidermis. The glycoprotein contains 4.5 mg. per cent of carbohydrate in the form of amino

sugar and also a sulfate radical. It is believed that it consists of chondroitin sulfate linked to a protein. This hypothesis is substantiated by the fact that the glycoprotein shows marked metachromasia following thionin staining of the paper strips, which is destroyed by testicular hyaluronidase and malt diastase. The nucleoprotein gives a positive Feulgen reaction.

The sources of these proteins have been investigated in sections of psoriatic scales by histochemical methods.

It is suggested that the demonstration of these proteins on paper strips may be used as a diagnostic and prognostic tool in psoriasis.

Comparative paper electrophoretic studies have been performed on extracts of normal epidermis, callus, and scales from nonpsoriatic exfoliative dermatitis. Glycoprotein was extracted in small amounts from the epidermal extracts and in larger amounts from the scales of exfoliative dermatitis, but not from callus. A fibrous protein and nucleoprotein were isolated from normal epidermis, but not from the other sources.

The possible significance of these findings in the pathogenesis of psoriasis has been discussed.

References

1. Willan, R. 1808. On Cutaneous Diseases. J. Johnson. London, England.
2. Flesch, P. & E. C. Jackson Esoda. 1957. Deficient water-binding in pathological horny layers. J. Invest. Dermatol. **28**: 5–13.
3. Grüneberg, T. & A. Szakall. 1955. Über den Gehalt an Schwefel und wasserlöslichen Bestandteilen in der verhornten Epidermis bei normaler und pathologischer Verhornung (Psoriasis). Arch. klin. u. exptl. Dermatol. **201**: 361–377.
4. Braun-Falco, O. 1957. Das Wesen des parakeratotischen Verhornungsmodus aus histochemischer Sicht. Klin. Wochschr. **35**(23): 1182–1184.
5. McMeekin, T. L. 1939. Serum albumin 1. The preparation and properties of crystalline horse serum albumin of constant solubility. J. Am. Chem. Soc. **61**: 2884.
6. Block, R. J., E. L. Durrum & G. Zweig. 1958. A Manual of Paper Chromatography and Paper Electrophoresis. 2nd ed. : 576–577. Academic Press. New York, N. Y.
7. Roe, D. A. 1957. Problems in the biochemistry of acantholysis. *In* Proc. 11th Intern. Congr. Dermatol. In press.
8. Flesch, P. & E. Kun. 1950. A colorimetric method for determination of sulfhydryl groups in tissue homogenates by 1-(4-chloro-mercuriphenylazo)-naphthol-2. Proc. Soc. Exptl. Biol. Med. **74**: 249–251.
9. Koiw, E. & A. Gronwall. 1952. Staining of protein-bound carbohydrates after electrophoresis of serum on filter paper. Scand. J. Clin. Lab. Invest. **4**: 244–246.
10. Drevon, B. & R. Donikan. 1955. Bull. soc. chim. biol. **37**: 1321–1325.
11. Winzler, R. J. 1955. Determination of serum glycoproteins. Methods of Biochemical Analysis. **2**: 279–311.
12. Partridge, S. M. 1948. Filter paper chromatography of sugars. Part I. Biochem. J. **42**: 238–250.
13. Payne, W. J. & R. Kieber. 1954. The chromatographic determination of glucosamine with ninhydrin. Arch. Biochem. Biophys. **52**: 1–4.
14. Burma, D. P. 1953. Electrochromatography on paper. Anal. Chim. Acta. **9**: 518–524.
15. Partridge, S. M. 1949. Aniline phthalate as a spraying reagent for chromatography of sugars. Nature. **164**: 443.
16. Hanes, C. S. & F. A. Isherwood. 1949. Separation of the phosphoric esters on filter paper chromatograms. Nature. **164**: 1107 1112.
17. Lillie, R. D. 1954. Histopathologic Technic and Practical Histochemistry. : 286; 292. Blakiston. New York, N.Y.

18. Lison, L. 1935. La significance de la métachromasie. Compt. rend. soc. biol. **118**: 821–824.
19. Hale, A. J. 1957. Histochemistry of polysaccharides—factors influencing metachromasia. Intern. Rev. Cytol. **6**: 193–263.
20. Roe, D. A. 1956. A fibrous keratin precursor from the human epidermis. J. Invest. Dermatol. **27**: 1–8.
21. Matoltsy, A. G. & C. A. Balsamo. 1955. The components of the cornified epithelium of the human skin. J. Invest. Dermatol. **25**: 71.
22. Partridge, S. M. 1948. The chemistry of connective tissues. I. The state of combination of chondroitin sulfate in cartilage. Biochem. J. **43**: 387–397.
23. Highberger, J. H., J. Gross & F. O. Schmitt. 1951. The interaction of mucoprotein with soluble collagen, an electron microscope study. Proc. Natl. Acad. Sci. **37**: 286–291.
24. Birbeck, M. S. C. & E. H. Mercer. 1957. Electron microscopy of the human hair follicle. I. Introduction and the hair cortex. J. Biophys. Biochem. Cytol. **3**(2): 203–213.
25. Montagna, W. 1956. The Structure and Function of Skin. Academic Press. New York, N. Y.
26. Richards, A. G. 1951. The Integument of Arthropods. Univ. Minn. Press. Minneapolis, Minn.
27. Hill, D. L. 1945. Carbohydrate metabolism during embryonic development (Orthoptera). J. Cellular Comp. Physiol. **25**: 205–216.
28. Trim, A. R. H. 1941. Studies in the chemistry of the insect cuticle. Biochem. J. **35**: 1088–1098.
29. Rudall, K. M. 1955. The distribution of collagen and chitin. Symposia Soc. Exptl. Biol. **9**: 49–70.
30. Van Oosten, J. 1957. The Skin and Scales in the Physiology of Fishes. **1**: 207–244. Academic Press. New York, N. Y.

CHEMICAL CHANGES IN PSORIATIC SCALES*

By Peter Flesch and Elizabeth C. Jackson Esoda

Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Systematic chemical analysis of the horny layer is a relatively recent development in the study of psoriasis. This is somewhat surprising, especially if we consider that so many other organs and systems have been subjected to detailed investigation. One of the main reasons for these delayed studies seems to be the fact that the chemical composition of normal horny layers was also unknown and, therefore, no basis of comparison was available. It is due to the development of new techniques and to the painstaking spade work of a number of scientists[1-13] that the time has finally arrived for the study of pathological horny layers.

Psoriatic scales offer many advantages for chemical studies. They are available in large quantities; an exfoliative case may produce several grams of scales daily. Their composition is remarkably constant. In our experience, washing[14] and most of the topical therapeutic measures have no appreciable effect on the components we have studied. As a rule, scales can be obtained in reasonably pure form, free from admixture with other tissues—an important consideration in the case of a heterogeneous tissue like the skin. On the other hand, psoriatic epidermis is not available in unlimited quantities; even if it were, it is unlikely that the cellular layers could be separated from the highly uneven dermal papillae and the strongly adherent horny layer.

Extensive chemical studies of the scales have been initiated by Grüneberg and Szakall.[15] These authors were among the first to comment on the constancy of the chemical data. This constancy was in sharp contrast with such unpredictable and inconstant features of the disease as the composition of the serum proteins. The scales consistently reflect certain anomalies, even though the nature of the underlying disturbances is obscure. In these studies special attention has been paid to the essential role of the soluble components of the horny layer. In contrast to hair or nail, which are built almost entirely of keratin, the horny layer consists of only about 60 or 70 per cent of water-insoluble horny framework; a large part of the remainder is soluble in water.[8, 16]

These water-soluble compounds perform most of the essential protective functions of the skin surface. They maintain its *p*H, regulate the flow of water and bind moisture, protect against ultraviolet light, and help in detoxification.[16] It is among these components that anomalies occur in psoriasis.

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Whether abnormalities exist in the psoriatic keratinous framework as well remains to be investigated.

We have studied the behavior of the following water-soluble chemical groups and components in aqueous extracts of pulverized, defatted psoriatic scales; free amino nitrogen, water-soluble proteins, free sulfhydryl groups, total pentoses, and free reducing substances.

Free Amino Nitrogen

The free amino nitrogen is consistently decreased in psoriatic scales. Normal values are 378 mg. per cent in normal horny layer and 178 to 207 mg. per cent in callus (8 determinations). In 24 cases of psoriasis the values for

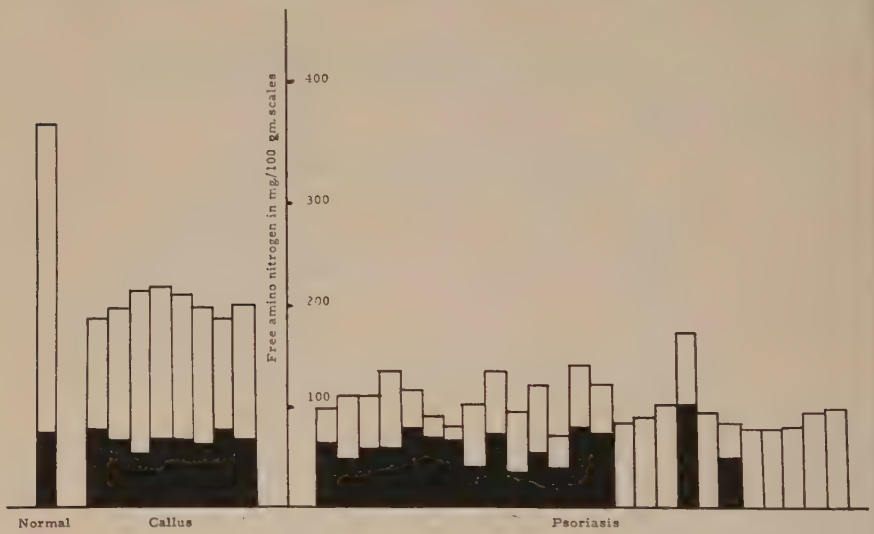

FIGURE 1. Free amino nitrogen in normal horny layer, callus, and psoriatic scales. Total heights of columns indicate amounts in untreated horny layers before extraction with water; black bars represent values in insoluble residue (keratin). Where black bars are absent, insufficient material was available for complete analyses.

free amino nitrogen ranged from 72 to 141 mg. per cent. The decrease is limited to the soluble fraction of the scales and, therefore, is strikingly reflected in the aqueous extracts of normal and psoriatic horny layers. In extracts of normal horny layers the free amino nitrogen content is 304 mg. per cent, in extracts of callus 124 to 157 mg. per cent (9 determinations), and in extracts of psoriatic scales 22 to 72 mg. per cent (6 determinations), as shown in FIGURE 1.

The low free amino nitrogen seemed to remain constant, regardless of the stage and severity of the disease. In an early case of a few weeks' duration with minimal scaling, the free amino nitrogen was decreased to 78 mg. per cent. External application of tar or of ammoniated mercury had no influence on the amino nitrogen content of the scales studied.

The constancy of the values may be due to the remarkable firmness with which these components are held in the meshes of the horny layer. This cohesiveness may be attributed to chemical and physical factors. As pointed out previously, it is impossible to leech out the water-soluble components of the horny layer without previous defatting. This observation suggests that they are shielded by a lipoid framework. In addition, pulverization of the scale is also essential for liberating all the soluble free amino nitrogen.

The lowered amount of amino nitrogen is probably a reflection of a decrease in the free amino acid content of the psoriatic horny layer. The anomaly is solely quantitative; there is unanimous agreement that there is no change in the qualitative composition of the free amino acids.[15, 17-19]

FIGURE 2. Schematic illustration of 0.1 mm. deep cut parallel to the surface in normal and psoriatic epidermis. Stippled areas represent cellular components. The much smaller amounts of cells obtained from psoriatic epidermis by this procedure may explain the low proteolytic enzymatic activity in psoriatic epidermis.[20]

The biochemical basis for the decreased free amino nitrogen content is unknown. Paschoud *et al.*[20] postulated that there was deficient activity of the proteolytic enzymes in the psoriatic epidermis. Their findings were based on *in vitro* assays of proteolytic enzymes in sections of psoriatic skin 100 μ thick, which were cut parallel to the surface. They observed an approximate 50 per cent decrease in enzyme activity in the diseased areas as compared with nonaffected and normal skin.[20] The conclusion that this decrease is due to deficient proteolytic activity is open to doubt. The authors did not take into account the fact that in psoriatic lesions the dermal papillae almost reach the surface in many places; hence, in sections cut parallel to the surface, the enzymatically active epidermal specimens will be contaminated with portions of inactive dermis and horny layer. The inclusion of the inert corium and horny layer in the sections of psoriatic skin may simulate a reduction of proteolytic activity (FIGURE 2).

Soluble Proteins

A surprisingly large portion of the psoriatic horny layer consists of soluble proteins. These proteins can be precipitated regularly by boiling the aqueous extracts of psoriatic scales. Under these conditions extracts of callus yield only traces of heat-coagulable substances (FIGURE 3).

The proteins precipitated in this way form a white stringy network that is characteristic of the disease. At present it is difficult to decide whether these proteins originate solely in the epidermis. The possibility must be considered that at least some of the soluble proteins arise from the corium and reach the horny layer through the thinned psoriatic epidermis. It seems, however, that most of the proteins result from a deranged epidermal metabo-

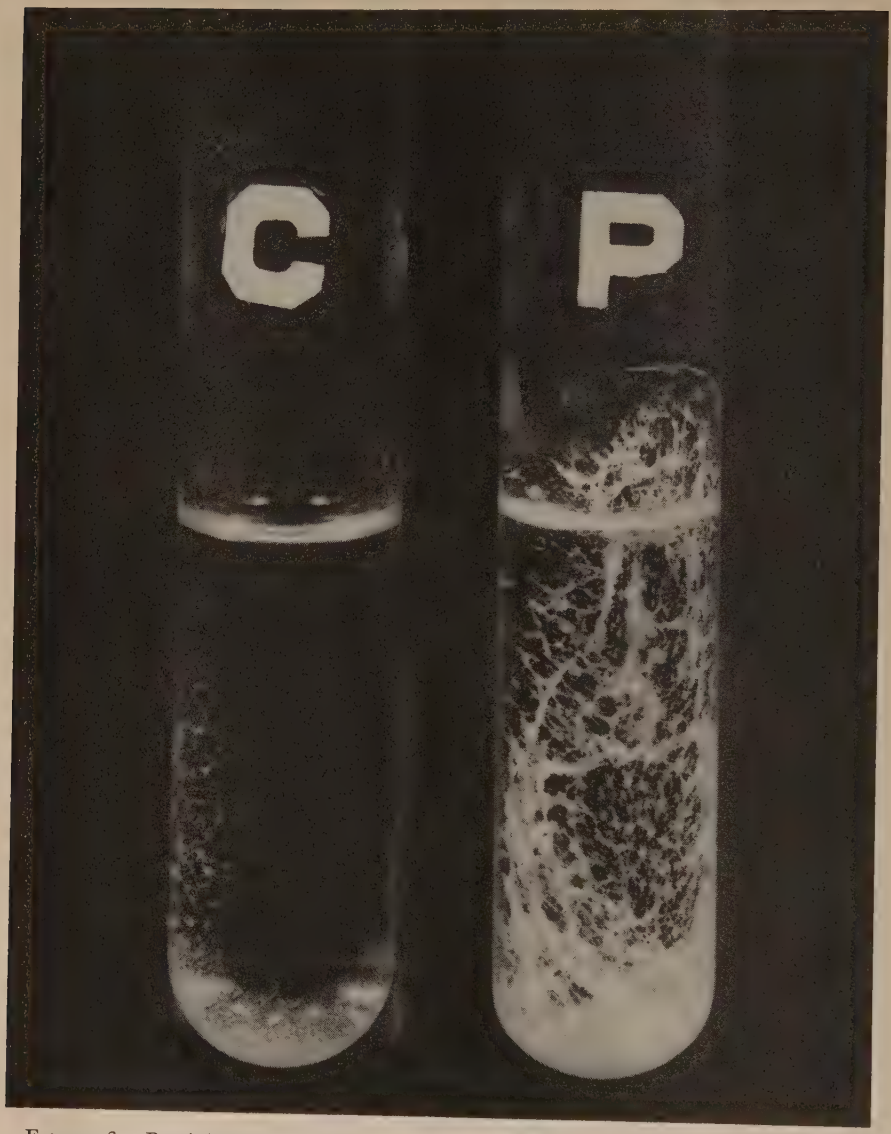

FIGURE 3. Precipitation of soluble proteins by boiling similar extracts of callus (C) and psoriatic scales (P). Note heavy white stringy precipitate in extract of psoriatic scales.

lism. Soluble proteins occur in macroscopically nonexudative scales; their chemical nature also indicates that they are the products of epidermal cells, rather than of mere exudation. Although proteins can be precipitated by boiling the extracts of scales from exfoliative dermatitis, the precipitate is usually granular and not stringy.

Sulfhydryl Groups

A sign of the increased soluble proteins is the high sulfhydryl content of the psoriatic scales. This phenomenon was first described by Zingsheim[21] and has since been amply confirmed.[22, 23] In our recent series of 18 cases the sulfhydryl content ranged from 52 to 251 mM $\times$ 10^{-2}/100 gm. In 8 cases callus contained 15 to 41 mM $\times$ 10^{-2} (FIGURE 4).

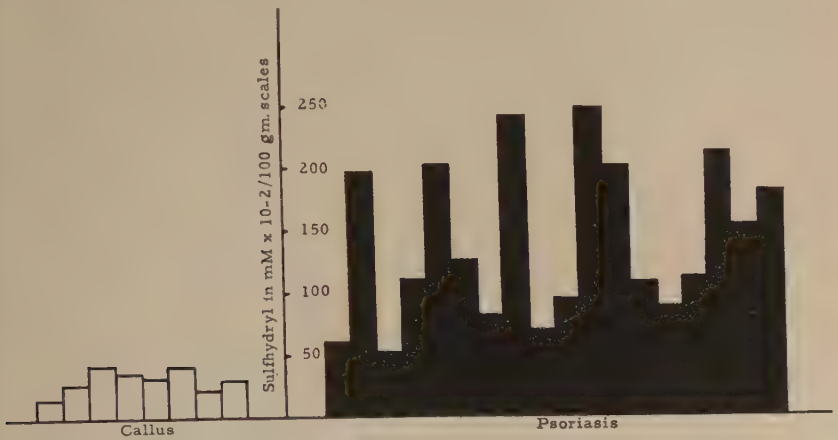

FIGURE 4. Sulfhydryl content in normal and psoriatic horny layers.

All the free sulfhydryl is bound to soluble proteins in the horny layer. When aqueous extracts of psoriatic scales are dialyzed, none of the sulfhydryl crosses the dialyzing membrane (TABLE 1).

It is premature to ascribe a definite role to these sulfhydryl-containing proteins in the pathogenesis of psoriasis. Various theories relating the high sulfhydryl content to incomplete keratinization are open to question.[23, 24] Our own tentative interpretation is based on the working theory that, during the consolidation of epidermal keratin, a fibrous precursor in the Malpighian cells combines with a sulfur-containing globular protein.[25, 26] The high sulfhydryl content could be a reflection of incomplete combination in the later stages of keratinization.

The high sulfhydryl content is the least specific of the chemical changes studied by us. Whenever the horny layer is formed at a more rapid rate, its sulfhydryl content rises. Therefore, the test does not distinguish between

TABLE 1

SULFHYDRYL IN EXTRACT OF PSORIATIC SCALE

Sulfhydryl in mM $\times$ 10^{-2}/100 gm. Scale

Scales: 60	Aqueous extract before dialysis: 58	Aqueous extract after dialysis: 53	Dialyzing fluid: 0

different types of exfoliative dermatitis. In our series all these cases had values ranging from 93 to 212 mM $\times$ 10^{-2}/100 gm.

After topical treatment with ammoniated mercury ointments the sulfhydryl groups disappear. This effect persists for several weeks, even after cessation of therapy.

Pentoses and Free Reducing Substances

The increased pentose content in extracts of psoriatic scales was first mentioned by Buckup and Szakall.[27] In their estimation, normal values are 0.3 to 1 mg./100 gm. as compared with 3 mg. per cent and more in psoriasis. In our series of 15 cases of psoriasis the total pentose level, as determined

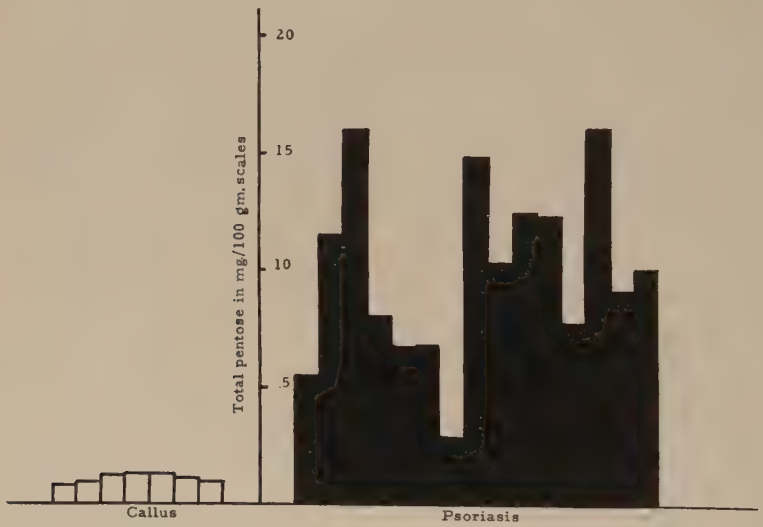

FIGURE 5. Total pentose in aqueous extracts of callus and psoriatic scales.

with orcinol,[28] ranged from 2.6 to 16 mg./100 gm. in the aqueous extracts of psoriatic scales. In 7 cases, extracts of callus contained 0.7 to 1.3 mg./100 gm. (FIGURE 5). The total pentose was increased to 16 mg. per cent in an early case with minimal scaling.

The total pentose concentration seems to fluctuate with the stage of the disease. In an exfoliative case of psoriasis the pentose content rose as the clinical status of the patient improved.

In all probability, the increased pentose reflects the abnormal nuclear metabolism of the psoriatic epidermis.

The change in total pentoses is not specific for psoriasis; we found it in scales from Darier's disease, in seborrheic dermatitis, in exfoliative dermatitis of unknown origin, and in two cases of mycosis fungoides. Buckup and Szakall[27] described elevated total pentose values in the uninvolved skin of subjects with chloracne and occupational eczema.

Although high total pentose occurs in a number of conditions, the free pentose is more specific for psoriasis. Psoriatic scales contain high amounts of free reducing substances. In 11 cases the values ranged from 1.2 to 2.7 mg. per cent, as compared with 0.4 to 0.6 mg. per cent in extracts of callus (FIGURE 6). Increased values of reducing substances were found in nonpsoriatic exfoliative dermatitis and in Darier's disease as well. However, it seems that in psoriasis a large portion of the free reducing substance is in the form of pentose, while glucose is more predominant in the other scaling conditions tested.

The high free pentose content in psoriatic scales forms the basis of a simple spot test for the diagnosis of the disease. The test is a modification

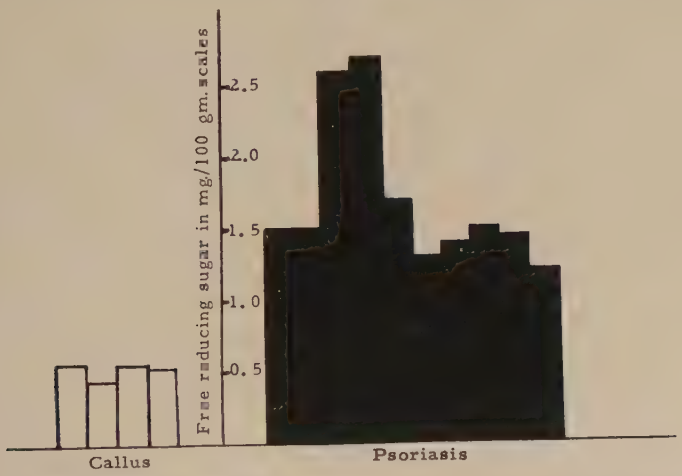

FIGURE 6. Free reducing substances in aqueous extracts of callus and psoriatic scales.

of the aniline phthalate color test[29] for the paper chromatographic identification of sugars. When defatted psoriatic scales are soaked overnight with water, the aqueous extract gives the brick-red or purple color of pentoses after heating with the reagent. Extracts of scales from other conditions produce an olive-green to light brown color characteristic of varying mixtures of glucose with pentose (FIGURE 7, see FRONTISPIECE). The advantage of the aniline phthalate test is its simplicity. A positive test is compatible with the disease, although probably not specific for it; in the absence of a positive test for pentoses, the chemical diagnosis of psoriasis should be rejected.

Discussion

The deranged chemical features in the water-soluble portion of psoriatic scales reflect a faulty epidermal metabolism. At present we have no conclusive evidence concerning the identity of the impaired epidermal enzyme systems. Consequently, it is premature to ascribe the abnormal chemical features of the psoriatic horny layer to definite cellular dysfunctions. Cer-

tain possible relationships may emerge. For example, the low free amino nitrogen could result from impaired activity of proteolytic enzymes; the nature and increased concentration of soluble proteins and the elevated sulfhydryl content could be based on insufficient consolidation of epidermal keratin, while the increased pentoses are probably the by-products of incomplete nuclear decomposition, as manifested also by the parakeratosis. These relations must be further investigated, however, before they can be considered as definitely proved.

We are on equally uncertain ground when we try to correlate the abnormal chemical features with the physical characteristics of the psoriatic horny layer. Psoriatic scales are abnormal in at least two respects: they are dry and sticky. The dryness is manifested by the low water-binding ability of the scales and their isolated extracts.[14] The stickiness or cohesiveness of the horny layer is the most conspicuous cutaneous feature of psoriasis. Normally the skin surface flakes off in invisible particles. Apparently the horny layer is broken into individual cells, which are cast off without any visible trace.[1, 30] In psoriasis the horny layer fails to break up. The cells stick together and adhere to the underlying cellular layers, forming the large, coherent silvery plaques characteristic of the disease. It would be an important step forward if we could definitely assign the dryness and the stickiness to specific chemical disturbances.

There are very few clues available. In our experience, the low water-binding ability of the scales and of their isolated extracts is invariably linked with a decreased free amino nitrogen content. This applies not only to psoriatic scales, but also to the dry horny layer of ichthyosiform erythroderma. On the other hand, in cases of ichthyosis vulgaris and keratoderma plantare, a normal water-binding ability goes hand in hand with a normal or nearly normal, free amino nitrogen content. Beyond this finding, the exact chemical nature of the hygroscopic components in the horny layer remains a mystery. The recent theory of Szakall,[31] ascribing at least some of the water-holding capacity to chemical combinations between pentoses and amino acids, remains to be confirmed. Some of the chemical findings in psoriatic scales—notably the low, free amino nitrogen and the high free pentose—could be interpreted as indicating a deficient combination of these components.

Stickiness of scales in general may or may not be associated with dryness. Any enhanced production of the horny layer causes the appearance of visible scales, as in dandruff or postultraviolet erythema. In contrast to the dryness, which seems to indicate the absence of some essential components, stickiness probably results from the presence of an abnormal substance. This assumption is supported by the following experiment. When an oily fluid is passed through a standardized column of powdered psoriatic scales, the flow rates are extremely prolonged, as compared with values obtained in powdered callus. After extraction with water, or even more so with dispersing agents such as allantoin or urea, the abnormal flow rates are accelerated. However, these accelerated rates do not reach those observed in pulverized callus.[32] We do not know the nature of the sub-

stance that holds the cells together and retards the flow of liquids. In the corium, similar cementing functions are performed by mucopolysaccharides. In psoriatic horny layers the abnormal presence of mucopolysaccharides has been demonstrated by histochemical[33] and direct chemical methods.[34] After treatment with hyaluronidase, the flow rates through some powdered scales are greatly accelerated. Whether mucopolysaccharides alone are responsible for the stickiness of psoriatic scales remains to be proved.

Even though the biochemical basis and the clinical significance of the chemical changes in the psoriatic horny layer are uncertain, the consistent occurrence of these anomalies opens up new possibilities for future research. Analysis of the scales has enriched our heretofore subjective, visual diagnostic tools with objective, quantitative methods. In quite a few cases we were able to make a differential diagnosis between psoriasis and other types of exfoliative dermatitis from the chemical composition of the scales alone, without ever having seen the patient. Furthermore, the realization that the water-soluble components are anomalous in psoriatic horny layers undoubtedly will speed up the search for further anomalous components in this fraction.[35] Thus the way is paved toward improved methods of diagnosis and better insight into the pathogenesis of the disease. This approach holds great promise for the future, as Szakall has pointed out.[27] We are no longer dealing with remote systems or organs. Our main concern is the anomaly in the skin that causes so much suffering for the millions of people afflicted by this enigmatic and incurable disease.

Summary

Aqueous extracts of psoriatic scales show the following consistent and characteristic chemical anomalies: (1) decreased free amino nitrogen without demonstrable change in the qualitative composition of the amino acids; (2) a large rise in soluble proteins; (3) an increase in the content of sulfhydryl groups which are all in the soluble protein fraction; (4) a higher total pentose value; and (5) elevated reducing substances, primarily in the form of pentose.

The high pentose content forms the basis of a simple spot test with aniline phthalate for the diagnosis of the disease.

None of these changes are specific for psoriasis. Nevertheless, the combination of these features is sufficiently characteristic to enable us to reject the diagnosis of psoriasis in their absence.

The possible clinical and biochemical significance of these findings is discussed.

Acknowledgments

We are greatly indebted to Daphne Anderson Roe of the Department of Physiology, Vassar College, Poughkeepsie, N. Y., for her helpful advice, and to Chesebrough-Pond's, Inc., New York, N. Y., for this firm's assistance and cooperation.

References

1. Rothman, S. 1954. Physiology and Biochemistry of the Skin. Univ. Chicago Press. Chicago, Ill.

2. Szakall, A. 1955. Über die Eigenschaften, Herkunft und physiologischen Funktionen der die H-Ionenkonzentration bestimmenden Wirkstoffe in der verhornten Epidermis. Arch. klin. u. exptl. Dermatol. **201:** 331–360.
3. Müting, D., H. Langhof & V. Wortmann. 1955. Die Aminosäurezusammensetzung gesunder menschlicher Haut. Z. klin. Med. **152:** 495–499.
4. Pascher, G., G. V. Steinbrück & H. W. Spier. 1957. Die wasserlöslichen Bestandteile der peripheren Hornschicht. V. Zur inhomogenen Verteilung von α-Amino-Stickstoff, Milchsäure, Chlorid, Kalium (und Natrium) im Stratum disjunctum. Arch. klin. u. exptl. Dermatol., **204:** 140–150.
5. Matoltsy, A. G. & C. A. Balsamo. 1955. A study of the components of the cornified epithelium of human skin. J. Biophys. Biochem. Cytol. **1:** 339–360.
6. Roe, D. A. 1956. A fibrous keratin precursor from the human epidermis. J. Invest. Dermatol. **27:** 1–8.
7. Ward, W. H. & H. P. Lundgren. 1954. The formation, composition and properties of the keratins. Advances in Protein Chem. **9:** 243–297.
8. Spier, H. W. & G. Pascher. 1955. Die wasserlöslichen Bestandteile der peripheren Hornschicht (Hautoberfläche). Quantitative Analysen. I. Allgemeine stickstoffhaltige Substanzen. Arch. Dermatol u. Syphilis. **199:** 411–427.
9. Spier, H. W. & G. Pascher. 1955. Die wasserlöslichen Bestandteile der peripheren Hornschicht (Hautoberfläche). Quantitative Analysen. II. Stickstoff-freie Säuren und Basen. Arch. Dermatol. u. Syphilis. **201:** 181–192.
10. Pascher, G. 1956. Die wasserlöslichen Bestandteile der peripheren Hornschicht (Hautoberfläche). Quantitative Analysen. III. α-Pyrrolidoncarbonsäure. Arch. klin. u. exptl. Dermatol. **203:** 234–238.
11. Pascher, G. & H. W. Spier. 1956. Die wasserlöslichen Bestandteile der peripheren Hornschicht (Hautoberfläche). Quantitative Analysen. IV. Die Ursache der Thermolabilität des Oberflächen-*p*H. Arch. klin. u. exptl. Dermatol. **203:** 239–245.
12. Spier, H. W. & G. Pascher. 1955. Freie Aminosäuren der Hautoberfläche. Quantitative Untersuchungen zur Frage ihrer physiologischen Bedeutung. Arch. Dermatol. u. Syphilis. **200:** 59–66.
13. Spier, H. W. & G. Pascher. 1956. Zur analytischen und funktionellen Physiologie der Hautoberfläche. Hautarzt. **7:** 55–60.
14. Flesch, P. & E. C. J. Esoda. 1957. Deficient water-binding in pathologic horny layers. J. Invest. Dermatol. **28:** 5–13.
15. Grüneberg, T. & A. Szakall. 1955. Über den Gehalt an Schwefel und wasserlöslichen Bestandteilen in der verhornten Epidermis bei normaler und pathologischer Verhornung (Psoriasis). Arch. klin. u. exptl. Dermatol. **201:** 361–377.
16. Stüpel, H. & A. Szakall. 1957. Die Wirkung von Waschmitteln auf die Haut. Dr. Alfred Hüthig. Heidelberg, Germany.
17. Hähnel, R. 1957. Die-N-endständigen Aminosäuren in der normalen Hornschicht und in Psoriasisschuppen. Arch. klin. u. exptl. Dermatol. **205:** 75–78.
18. Flesch, P. & E. C. J. Esoda. 1957. Simple tests for the demonstration of the low free amino nitrogen content in psoriatic scales. J. Invest. Dermatol. **29:** 247–249.
19. Matoltsy, A. G. Unpublished experiments.
20. Paschoud, J. M., W. Keller & B. Schmidli. 1956. Untersuchungen über Peptidasen in der gesunden und befallenen Haut von Psoriasiskranken. Arch. klin. u. exptl. Dermatol. **203:** 203–216.
21. Zingsheim, M. 1952. Die Rolle freier Sulfhydrylgruppen bei der Schuppenflechte. Deut. med. Wochschr. **77:** 1630–1631.
22. Van Scott, E. J. & P. Flesch. 1954. Sulfhydryl groups and disulfide linkages in normal and pathological keratinization. Arch. Dermatol. and Syphilol. **70:** 141–154.
23. Magnus, I. A. 1956. Observations on the thiol content of abnormal stratum corneum in psoriasis and other conditions. Brit. J. Dermatol. **68:** 243–251.
24. Ligterink, J. H. 1955. The mechanism of cornification in parakeratosis, particularly in psoriasis. Dermatologica. **111:** 301–312.
25. Flesch, P. 1956. Biochemical data on physiological and pathological keratinization. J. Soc. Cosmetic Chemists. **7:** 521–530.

26. Flesch, P. 1958. Chemical data on human epidermal keratinization and differentiation. J. Invest. Dermatol. **31**: 63–73.
27. Buckup, H. & A. Szakall. 1957. Über typische Veränderungen des Gehaltes von Hornschichtextrakten an Lipoiden und Pentosen bei verschiedenen Gewerbedermatosen. Gewerbedermatosen. **5**: 181–191.
28. McRary, W. L. & M. D. Slattery. 1945. Colorimetric determination of pentose and pentosans. Arch. Biochem. **6**: 151–156.
29. Partridge, S. M. 1949. Aniline hydrogen phthalate as a spraying reagent for chromatography of sugars. Nature. **164**: 443.
30. Rothman, S. 1956. Physiology and pathology of keratinization. J. Soc. Cosmetic Chemists. **7**: 576–583.
31. Szakall, A. 1957. Symposium. The Biology of the Skin Surface. 11th Intern. Congr. Dermatol. Stockholm, Sweden.
32. Flesch, P. & E. C. J. Esoda. 1957. Defective epidermal protein metabolism in psoriasis. A.M.A. Arch. Dermatol. **76**: 393–401.
33. Braun-Falco, O. Personal communication.
34. Roe, D. A. Unpublished experiments.
35. Dihlmann, W. 1957. Untersuchungen über die Giftigkeit von Extrakten und Dialysaten von Psoriasis-Efflorescenzen. Arch. klin. u. exptl. Dermatol. **205**: 186–195.

OBSERVATIONS ON THE PROBLEM OF PATHOGENESIS IN PSORIASIS

By Allan L. Lorincz

Section of Dermatology, Department of Medicine, University of Chicago, Chicago, Ill.

Over the years an ever-increasing wealth of fundamental, essentially descriptive information about psoriasis has become available from clinical, histopathological, biochemical, and physiological viewpoints. However, thus far we have neither etiological nor pathogenetic understanding of this common disease except in incomplete general terms. In such general terms, the psoriatic process can be viewed fundamentally as involving pathological acceleration of epidermopoiesis.

By analogy with erythropoiesis, the continuous, physiological process of proliferation, maturation, and specialized functional death of epidermal cells in the process of keratinization can aptly be termed epidermopoiesis.[1] In addition to histological acanthosis and increased epidermal mitotic activity, a number of local metabolic consequences accompany the pathologically accelerated turnover of epidermal cells in psoriasis.[2] As shown by Gans and his associates[3-5] and by Buhmann,[6] oxygen consumption by psoriatic epidermis is strikingly increased. Although this increased consumption of oxygen is not qualitatively specific for psoriasis, it may exceed by severalfold (according to Gans) the increased epidermal oxygen consumption that occurs in other diseases involving this tissue, such as eczema and neoplasms. Furthermore, the accelerated metabolic activity of the epidermis is accompanied by various disturbances in the biochemical functions of the epidermis which, for the most part, are also not specific for psoriasis. Many of the abnormalities in the specialized areas of keratinization and esterification already have been presented in this monograph. An additional example of a biochemical disturbance accompanying accelerated keratinization involves phospholipid metabolism. In the lesions of psoriasis and other rapidly keratinizing disorders, Snider *et al.*[7] found that the hydrolytic decomposition of choline-containing phospholipids is accelerated in the horny layer, as indicated by an increase in the relative amount of free choline to total choline from normal levels of about 5 per cent to about 70 per cent. At the same time the physiological decomposition of choline during keratinization was found to be less complete the more keratinization was accelerated, as indicated by progressively higher total choline content of the scales.

It is of interest, as pointed out recently by Kúta and Neumann,[8] that psoriasis seems to have a predilection to appear on sites such as the elbows and knees, where the epidermal regeneration rate is particularly high, as had been shown by Fular[9] in his studies on the rapidity of self-cleaning of the skin after application of osmic acid stains. Furthermore, stimuli effective in eliciting the Koebner phenomenon in psoriasis appear to have as a common denominator their ability to stimulate epidermopoiesis. Stimuli that produce superficial inflammatory reactions, as well as those that directly injure

the epidermis and provoke regenerative repair, are effective in this regard. By way of contrast, the simple injury to superficial blood vessels that can be produced by suction on the skin and that is evidenced by superficial intracutaneous hemorrhage fails completely to be an effective Koebner stimulus, as beautifully demonstrated by Reinertson.[10] Conversely, agents or conditions that suppress epidermopoiesis or cellular proliferation tend, in general, to suppress psoriasis. Here can be listed the various empirically effective remedies for psoriasis such as tars, mercurial preparations, arsenic, and various ionizing radiations. Other perhaps more drastic cellular poisons such as folic acid antagonists, nitrogen mustards, cortisonelike steroids, and colchicine can similarly suppress psoriasis, as can severe protein deficiency induced by starvation or cachexia-producing illness. In a somewhat facetious broad sense, one can boil down the current empirical medicinal treatment of psoriasis almost to a process of selecting the best brand of poison.

Besides leading to the formation of characteristic parakeratotic scales, the accelerated, incomplete keratinization in psoriasis also results in a great increase in local insensible perspiration, as was elegantly shown by Rothman and Felsher.[11, 12] In part, this increase represents water released from epidermal cells as they undergo dehydration during keratinization. Calculations, however, show that epidermal cell dehydration cannot possibly account for the huge increase in insensible perspiration observed in psoriatic lesions. Therefore there must be at least some degree of damage to the major water barrier at the base of the stratum corneum. This barrier damage accompanying psoriasis may well have an autocatalytic effect on the disease process by permitting partial dehydration of the Malpighian layer which, as recently shown by Williams and Hunter,[13] is a potent stimulus for triggering epidermal regeneration. This dehydration effect may be one mechanism that favors peripheral enlargement of psoriatic lesions. The generally beneficial effects of high humidity and bland greases on psoriasis perhaps also can be understood in the light of this hypothetical autocatalytic dehydration effect.

Similarly, the inflammatory changes accompanying the psoriatic process may have a catalytic effect on the growth of lesions by stimulating epidermopoiesis.

Despite speculations such as these and the many descriptive facts available about psoriasis, the really fundamental question of the etiology or cause of the pathologically accelerated epidermal regeneration in psoriasis remains unanswered. We cannot with assurance even assume that psoriasis is an etiological entity, for it is conceivable that it may represent only a pattern of reaction to perhaps a whole series of quite different causes and that this pattern is conditioned by some constitutional anomaly, as perhaps might be suggested by the well-known hereditary predisposition to the disease. The occurrence of strikingly psoriasiform syphilids and psoriasiform eczematous reactions of various sorts also might tend to support this concept of a common reaction pattern to possibly multiple causes.

The general etiological theories for psoriasis that have received most consideration over the years are (1) that it represents an inherent or consti-

tutional metabolic disturbance, either systemic or limited to the skin; (2) that it is caused by some viral or other type of infectious agent to which only certain individuals react or are susceptible; or (3) that it is basically an allergic or autoimmune disease involving antibodies directed against some kind of antigens in the epidermis. Of course, these hypotheses need not be mutually exclusive.

Among points that argue against but do not exclude the inherent purely metabolic defect possibility are:

(1) The repeated failure, despite persistent intense efforts, to demonstrate consistently any such metabolic disturbance in psoriatic individuals.

(2) The striking inflammatory and vascular changes that accompany psoriasis lesions. Capillary microscopy, for example, reveals what is believed to be a characteristic and most spectacular tortuosity and elongation of papillary capillary loops in the lesions.[14, 15]

(3) The general clinical course of psoriasis, marked by intermittency and often by a sudden onset with widely distributed small lesions. As the disease recurs and evolves, the lesions tend to become more persistant, less generally distributed, and larger and figurated. This changing morphology of the cutaneous lesions is reminiscent of what occurs in treponemal diseases.

(4) The not infrequent association of psoriasis with systemic, rheumatoid manifestations.

In view of these objections to the inherent metabolic defect hypothesis, the infectious and/or allergic theories seem more attractive.

Among infectious agents, viruses, as early suggested by Lipschütz,[16] have been most considered as possible etiological agents for psoriasis. In view of the well-known difficulties in demonstrating some viruses, as well as in establishing their relationship to specific diseases, the failure thus far to find a psoriasis virus is not too strong an argument against this possibility. The recent claim of Ukhin[17] in Russia that psoriatic serum introduced into the skin locally inhibits the Koebner reaction to simultaneous scarification is of interest in regard to the viral hypothesis. Control injections of normal serum simultaneously in such individuals at other sites were done together with scarification to be sure that Koebner-reactive patients were being used. Confirmation of this unusual report is necessary, of course.

Further pathogenetic speculations about psoriasis and the Koebner phenomenon, as well as extensive lists of references to earlier literature on these subjects, appear in articles by Melczer[18] and Szodoray.[19]

References

1. Pinkus, H. 1954. Biology of epidermal cells. *In* Physiology and Biochemistry of the Skin. : 590. S. Rothman. Univ. Chicago Press. Chicago, Ill.
2. Schamberg, J. F., J. A. Kolmer, A. J. Ringer & G. W. Raiziss. 1913. Research studies in psoriasis. Am. J. Cutan. Dis. incl. Syph. **31**: 698.
3. Gans, O. 1923. Gewebsatmung und Röntgenwirkung. Deut. med. Wochschr. **49**: 16.
4. Gans, O. 1952. Some observations on the pathogenesis of psoriasis. Arch. Dermatol. and Syphilol. **66**: 598.
5. Steigleder, G. K. 1955. Zur Funktion der Acanthose. Arch. Dermatol. u. Syphilis. **200**: 377.

6. Buhmann, A. 1936. Atmung und Glykolyse in normaler und pathologisch veränderter Haut, insbesondere mit Hinblick auf Psoriasis. Biochem. Z. **287**: 145.
7. Snider, B. L., H. R. Gottschalk & S. Rothman. 1949. The fate of choline in normal and pathologic keratinization of the epidermis. J. Invest. Dermatol. **13**: 323.
8. Kúta, A. & E. Neumann. 1957. Koebner's phenomenon in a study concerning the primary epidermal pathogenesis of psoriasis. Dermatologica. **115**: 51.
9. Fular, W. 1953. Morphol. J. **96**: 1.
10. Reinertson, R. P. 1958. Vascular trauma and the pathogenesis of the Koebner reaction in psoriasis. J. Invest. Dermatol. **30**: 283.
11. Rothman, S. & Z. Felsher. 1944. Insensible perspiration and keratinization process. Proc. Soc. Exptl. Biol. Med. **56**: 139.
12. Felsher, Z. & S. Rothman. 1945. The insensible perspiration of the skin in hyperkeratotic conditions. J. Invest. Dermatol. **6**: 271.
13. Williams, M. G. & R. Hunter. 1957. Studies on epidermal regeneration by means of the strip method. J. Invest. Dermatol. **29**: 407.
14. Gilje, O., P. A. O'Leary & E. J. Baldes. 1953. Capillary microscopic examination in skin diseases. Arch. Dermatol. and Syphilol. **68**: 136.
15. Davis, M. J. & A. L. Lorincz. 1957. An improved technic for capillary microscopy of the skin. J. Invest. Dermatol. **28**: 283.
16. Lipschütz, B. 1910. Untersuchungen über Dermotropismus: Theorie der Psoriasis vulgaris. Wien. klin. Wochschr. Also, 1919. Untersuchungen über Psoriasis vulgaris. Arch. Dermatol. u. Syphilis. **127**: 849.
17. Ukhin, A. F. 1952. Phenomenon of suppression of isomorphous reaction during psoriasis. Vestnik Venerol. i Dermatol. **3**: 31.
18. Melczer, M. 1952. A Köbner-féle izgalmi tünet oka és keletkezési módja a bör halmozásos eredetü betegségei: a pexismosisok, vagy pexidermák—Egyik legfontosabb pexiderma: a psoriasis vulgaris. Orvosi Hetilap. **93**: 1087.
19. Szodoray, L. 1955. Nervale Faktoren im Pathomechanismus der Psoriasis. Arch. klin. u. exptl. Dermatol. **201**: 581.

POSSIBLE SIGNIFICANCE OF ELEVATED ARGINASE ACTIVITY IN PSORIASIS SCALES

By Simon Rothberg

Dermatology Service, General Medicine Branch, National Cancer Institute, Public Health Service, Bethesda, Md.

The enzyme arginase was first discovered in extracts of mammalian liver by Kossel and Dakin[1] in 1904. Subsequently the enzyme was found by many investigators to be present in the mammary gland, testis, and kidney of mammals, although in lesser amounts than in the liver. Not until 1948 was it found to be present in human skin. Mardashev and Semina[2] and Van Scott,[3, 4] working independently, established its presence in this organ, maximally concentrated in the epidermis.

Clementi,[5] Hunter and Dauphinee,[6] and Baldwin[7] have shown that arginase is present in the livers of vertebrates with a ureotelic metabolism, but absent in those vertebrates (birds) with a uricotelic metabolism. The functional role of liver arginase was unclear, however, until the classic experiments of Krebs and Henseleit.[8] These investigators found that, in rat liver slices, urea could be synthesized from ammonia and carbon dioxide, and that this synthesis was enhanced by the presence of catalytic amounts of ornithine and citrulline in the incubation medium. The Krebs-Henseleit ornithine cycle and its operation in the liver, according to present knowledge, are outlined in FIGURE 1.

The significance of arginase in the skin is unknown. The possibility exists that, of the ornithine cycle enzymes, only this enzyme is present in the epidermis and that it serves to produce ornithine and urea from arginine extrahepatically. If arginine synthetase also were present in epidermis, then a partial cycle might function in the epidermis, as in the kidney and testis, where arginine is synthesized from citrulline (step III of FIGURE 1) and is then enzymatically cleaved to ornithine and urea.

As arginine is one of the major constituents of keratin,[9-11] there is added significance in its presence in the epidermis. However, the specific relationship of arginase to the incorporation of arginine or ornithine into the major protein of epidermis, keratin, has not been examined. A more detailed evaluation of levels of arginase activity in normal epidermal tissue, and comparison of these levels to those found in pathological epidermal tissue, would seem to be helpful for further investigations of other enzymes of the Krebs-Henseleit ornithine cycle in these tissues.

Materials and Methods

Collection and preparation of tissues. Scales from lesions of desquamatory skin diseases, stratum corneum of uninvolved skin of patients with psoriasis and of normal individuals, and stratum corneum of normal plantar skin and normal epidermis were obtained and prepared as previously described.[13]

Hair roots were obtained from manually epilated hairs of human scalp. By means of a fine scissors the hair root was cut from the remainder of the hair at the level of the distal end of the outer root sheath. The pooled hair roots were found to reach constant weight during their manipulation and were weighed* and assayed without further drying.

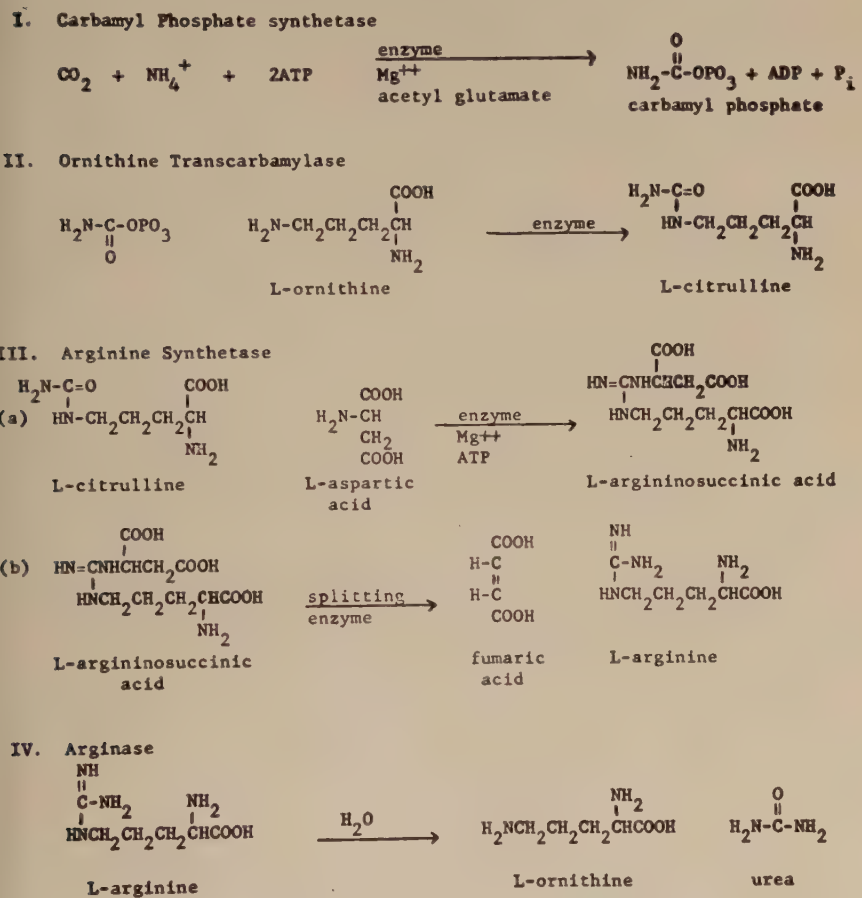

FIGURE 1. Steps in the Krebs-Henseleit ornithine cycle.

Arginase assay. Two types of arginase activity were determined,[4] potential and native. Potential arginase activity was obtained by first incubating 10 mg. of powdered tissue in 8 ml. of 0.05 M $MnCl_2$ for 1 hour at 50° C. The arginine hydrolysis was carried out at 37° C. for 10 min. following the addition of 2 ml. of 1.7 M arginine, *p*H 9.5. The reaction was terminated by the addition of 2 ml. of 1.2 N H_2SO_4, and the reaction flask was placed immediately in an ice bath. An aliquot was taken for the deter-

* Cahn electrobalance, Harshaw Chemical Co., Philadelphia, Pa.

mination of urea by the urease* method.[8] The carbon dioxide formed was measured manometrically at *p*H 5.0 in the Warburg apparatus at 38° C. according to standard procedure.[14]

Native activity was measured without prior activation of the enzyme with $MnCl_2$; instead, the tissue was incubated with water for 1 hour at 50° C. Appropriate controls were run as previously described.[13]

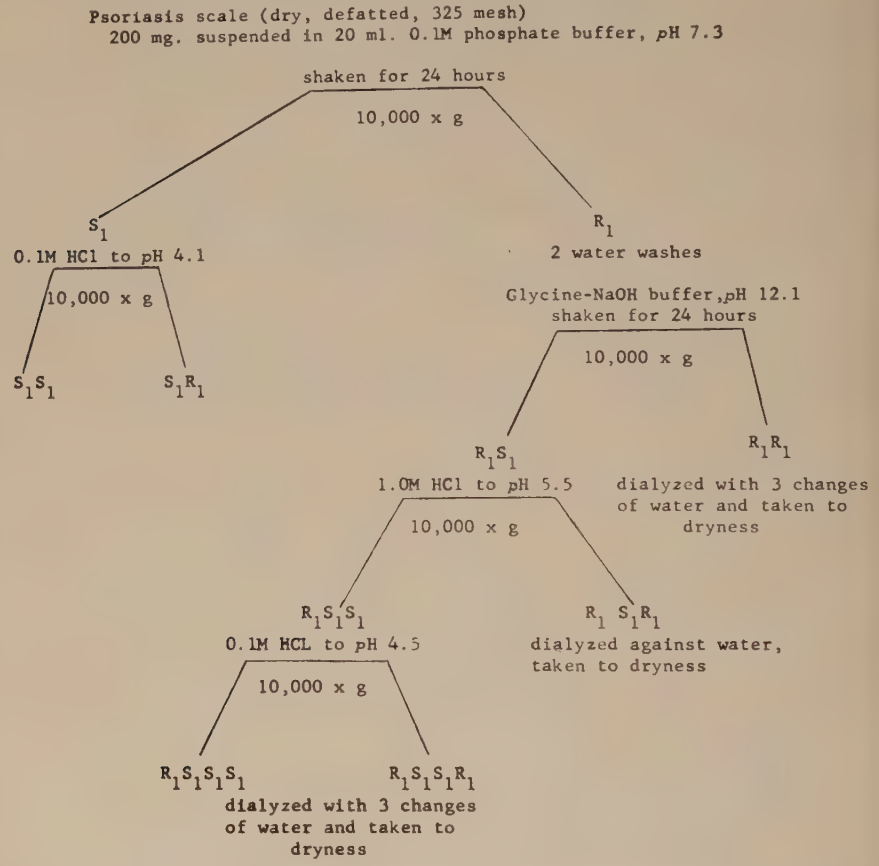

FIGURE 2. Procedure for preparing protein fractions from normal epidermal tissue and psoriasis scales.

The quantity of hair roots used for microarginase determinations was approximately one one-hundredth of that used in the usual assay (0.100 mg. instead of 10 mg.). Ornithine was measured in these analyses instead of urea in the usual assay. It was separated from the other basic amino acids by means of high-voltage paper electrophoresis† at *p*H 3.7[15] and was quanti-

* Urease was obtained from the Hartman and Leddon Co., Philadelphia, Pa., prepared fresh as a 1 per cent solution in 0.3 M acetate buffer, *p*H 5.0.

† Apparatus used through the courtesy of C. B. Anfinsen, Jr., National Heart Institute Public Health Service, Bethesda, Md.

ated by a modification[16] of the colorimetric method of Chinard.[17] The spots on the Whatman No. 3 paper were developed by dipping the paper in a freshly prepared acid ninhydrin solution consisting of 250 mg. ninhydrin, 10 ml. Chinard "A" (3 parts glacial acetic acid and 2 parts 6 M phosphoric acid), and 40 ml. acetone. The dried paper was developed by steaming in an autoclave (exhaust open) for 8 min. and drying therein for 1 min. The color was stabilized to an orange red by dipping in a copper solution.[18] Maximum density of the well-separated ornithine was measured with a Welch Densichron. The amount of ornithine was determined from a standardization curve of densities obtained from known amounts of ornithine simultaneously chromatographed on the same paper as the unknown.

Arginase activity was expressed as the milligrams of urea nitrogen formed per 100 gm. of dry, defatted tissue (with the exception of hair roots, which were not defatted) resulting from the hydrolysis of arginine upon incubation for 10 min. at 37° C.

Preparation of protein fractions from normal epidermis and psoriatic scales. FIGURE 2 represents the scheme used in preparing protein fractions from both normal human epidermis and psoriatic scales. The fractions S_1R_1, $R_1S_1R_1$, $R_1S_1S_1R_1$, R_1R_1, and $R_1S_1S_1S_1$ were dialyzed, dried, and separately sealed in glass tubes after the addition of 20 per cent HCl (1 ml. per 3 mg.). The tubes were heated for 20 hours in an oven maintained at 105° C. The hydrolysates, with water washings of the hydrolysis tubes, were transferred to lyophilization tubes and taken to dryness. The dried material was taken up in a small aliquot of water and again taken to dryness. The hydrolysates were then made to appropriate volumes (0.5, 1.0, or 2.0 ml.) according to the number of milligrams of protein hydrolyzed. In order to test for the presence of a single residue, or more, of ornithine in a molecule of epidermal keratin, aliquots containing 0.005 μM of protein were analyzed, assuming a molecular weight of 60,000 as found for wool.[12] These aliquots were spotted on Whatman No. 3 paper and run by high voltage electrophoresis and were further processed as described earlier.

Results

A previous report[13] describing the variation of arginase activity with particle size of powdered tissue clearly indicates the need for using only particles that pass through the 325 mesh screen. From TABLE 1 (patient M.S.) it is clear that the smaller particle size is most important in the case of psoriasis and mycosis fungoides, although it is less so for callus and normal epidermis.

The optimum incubation time for the activation of arginase, known to be variable in different tissues,[19] was found to be 1 hour in normal epidermis, psoriatic scales, and callus. Zero-order kinetics was found to govern the hydrolysis of the substrate, at least for the first 15 min. A reaction time of 10 min. was selected for hydrolysis.

Arginase activity of psoriatic scales, normal epidermis, and normal stratum corneum. The potential and native arginase activities were greater in scales of psoriasis than in any other tissue examined, with the exception of scales from skin involved with ichthyosiform erythroderma (TABLE 2). Activities

Table 1
Variation of Arginase Activity* with Particle Size

Sieve mesh	Microns	Psoriasis scales (M.S.)	Callus (M.S.)	Scales of mycosis fungoides	Epidermis
60	250	16,200	17,800	12,700	11,400
100	149	21,200	21,600	—	—
200	74	32,400	22,400	21,500	9,500
325	44	35,800	—	—	—
Regular†.....		23,400	21,900		

* Potential activity expressed as mg. of urea nitrogen per 100 gm. of dry, defatted tissue.
† Includes all sized particles passing through a 60-mesh sieve before further sieving.

Table 2
Arginase Activity* in Various Epidermal Tissues

Specimen	Potential activity	Native activity
Normal epidermis	7400	730
Stratum corneum, normal (V.S.)	7760	—
Stratum corneum, uninvolved, from patient with psoriasis (M.S.)	3160	310
Plantar callus (pooled)	22,400	1600
Scales, psoriasis (M.B.)	35,900	2310
Scales, psoriasis (A.A.)	48,700	2580
Scales, psoriasis (M.D.)	92,500	2860
Scales, psoriasis (L.P.)	36,900	2903
Scales, psoriasis (J.W.)	23,800	2685
Scales, psoriasis (A.S.)	34,500	2915
Scales, exfol. erythroderma (P.R.)	20,900	1150
Scales, nummular eczema (L.L.)	12,975	500
Scales, ichthyosiform erythroderma (R.H.)	27,625	2250
Scales, ichthyosis (M.C.)	19,100	1190

* Expressed as mg. of urea nitrogen per 100 gm. of dry, defatted tissue.

Table 3
Arginase Activity* of Different Keratin-Forming Areas on the Same Individual (M.S.)

	Potential	Native
Psoriasis scales (trunk)	35,900	2,310
Stratum corneum of uninvolved skin (trunk)	3,160	310
Stratum corneum of uninvolved plantar skin	17,700	1,710

* Expressed as mg. of urea nitrogen per 100 gm. of dry, defatted tissue.

of normal epidermis ranged between 3900 and 14,950, while those of psoriasis scales ranged between 23,800 and 92,500. Activities of normal stratum corneum and stratum corneum from uninvolved skin in patients with psoriasis were similar to those of normal epidermis.

TABLE 3 lists the potential and native arginase values of stratum corneum from different areas of a single individual with psoriasis. The activity of the psoriatic scales is tenfold that of uninvolved stratum corneum; the activity of plantar callus is sixfold that of uninvolved stratum corneum.

TABLE 4
INFLUENCE OF NORMAL EPIDERMIS UPON THE ARGINASE ACTIVITY* OF PSORIASIS SCALES

Tissue	Experimental	Calculated	Difference	Per cent inhibition
(A) Psoriasis (A.S.)	34,900	½A = 17,450		
(B) Normal epidermis	6,240	½B = 3,120		
(C) Mixed tissues (½A + ½B)	15,100	½A + ½B = 20,570	5,470	26.5

* Expressed as mg. of urea nitrogen per 100 gm. of dry, defatted tissue.

TABLE 5
ESTIMATED ARGINASE ACTIVITY* IN POOLED HUMAN HAIR ROOTS

System	Total μM of ornithine formed	Tissue wgt., mg.	Milligrams of urea nitrogen per 100 gm. of dry tissue
Complete †	0.054	0.270	1120
Complete	0.090	0.234	2150
Minus $MnCl_2$	0.0098	0.174	316
Minus $MnCl_2$	0.0112	0.210	299
Minus $MnCl_2$ and arginine	none	0.309	
Minus $MnCl_2$ and arginine	none	0.198	

* Expressed as mg. of urea nitrogen per 100 gm. of dry, defatted tissue.

† Weight tissue incubated with 0.2 ml. of 0.05 M $MnCl_2$ for 1 hour at 50° C. and hydrolyzed by adding 0.05 ml. of 1.7 M arginine, *p*H 9.5. The reaction was concluded by adding 0.05 ml. of 1.2 N H_2SO_4.

Inhibition of arginase activity by normal epidermis. The presence of an inhibitory substance in normal epidermis that decreases the high arginase activity of psoriatic scales was detected by mixed tissue experiments. The results of these experiments, shown in TABLE 4, indicate that the arginase activity of psoriatic scales is lowered in the presence of normal epidermal tissue.

Arginase of the hair root. Arginase activity was found, with the microtechnique, in hair roots (TABLE 5). As with the macro determinations of

arginase in the other tissues, the potential activity of arginase in this tissue was found to be several fold that of the native activity.

Ornithine in hydrolyzed protein fractions of normal epidermis and psoriatic scales. The use of high-voltage electrophoresis, coupled with a sensitive color reaction, permitted detection of small amounts of ornithine in the presence of twentyfold amounts of lysine. In all cases, the ornithine detected in the protein hydrolysates examined was less than that which would have been present had the molecular weight of the protein been 60,000 or less (TABLE 6).

TABLE 6
ORNITHINE IN HYDROLYSATES OF PROTEIN FRACTIONS OF NORMAL EPIDERMAL TISSUE AND PSORIATIC SCALE

Fraction	Aliquot μM protein	Experimental μM ornithine found	Theoretical μM ornithine for 1 residue
Normal epidermis			
$R_1S_1R_1$	0.00474	0.00349	0.00474
Psoriatic scale			
S_1R_1	0.00579	0.00100	0.00579
$R_1S_1R_1$	0.00412	0.00175	0.00412
$R_1S_1S_1R_1$	0.00438	0.00366	0.00438

Discussion

In the mammalian liver the enzymes of the Krebs-Henseleit ornithine cycle convert excess ammonia to urea. In the kidney and testis the cycle is known to be incomplete, only the arginase and arginine synthetase having been found. Preliminary enzymatic examination of psoriatic scales has indicated the presence of arginine synthetase.[16] This would suggest that the epidermis can synthesize arginine, as well as degrade it, and may function as an extrahepatic mechanism to remove excess ammonia.

The presence of increased *in vivo* arginase activity in scales of psoriasis, exceeding that of any other tissue examined, is evident from the data. It is not clear, however, whether this is due to a greater amount of enzyme (as the elevated potential activities may suggest) or whether it is due to the absence of an inhibitor such as that found in normal epidermis. This inhibitor apparently is either absent in scales of psoriasis or present in quantities insufficient to depress to any extent the arginase activity.

With increased arginase activity in psoriasis, the intracellular products of hydrolysis may be expected to reach concentrations exceeding those found in normal epidermis. One of the products, ornithine, differs from lysine only by one CH_2 group, and is otherwise similar in being a dibasic amino acid. Ornithine could possibly substitute for lysine in formation of the protein, keratin. If the substitution occurred at a critical location, essential bonding of the finished protein might be prevented, which would account for the physically abnormal stratum corneum found in psoriasis.

Ornithine was found to be present in the hydrolysates of the various epidermal protein fractions, but in all cases in amounts less than one residue per molecule if the molecular weight of the proteins was 60,000 or less. The ornithine appearing in the chromatograms probably resulted from the acid hydrolysis of arginine in the protein. This conclusion is supported further by the fact that separate acid hydrolysis of arginine alone caused 2 per cent of the arginine to be hydrolyzed to ornithine and urea.

Urea, another product of the enzymatic hydrolysis of arginine, might act intracellularly to cleave hydrogen bonds of protein molecules formed during keratinization. This possibility requires further exploration.

A comparison of arginase activity in stratum corneum from various areas of the body is of considerable interest. The difference between plantar callus and normal stratum corneum is in need of special emphasis. The widely different activities found indicate that these tissues, although having certain similarities, are chemically (as well as physically) different from each other. In addition to the enzymatic difference between the two tissues, they are further differentiated chemically in that plantar callus has considerably more protein-contained arginine than stratum corneum of the trunk.[20] These differences emphasize the necessity to consider each tissue individually at all times, and that, for example, the use of plantar callus is not warranted as a normal control tissue for comparison to pathological horny layers from areas of the body other than the sole.

The need for microtechniques in biochemical investigations of the skin and its appendages is more than apparent. Although analysis of powdered hair for arginase by the usual macrotechnique does not demonstrate the presence of enzyme, the enzyme has been found in pooled hair roots by the microtechnique. Only by further use of micro methods will the definitive biochemical characteristics of the various tissue components of the hair root be elucidated.

At present our knowledge of the true significance of arginase and its variant levels in normal and pathological epidermal tissues is not complete. Further study is necessary to demonstrate the role of the enzyme in the process of normal keratinization before final interpretation can be made of its role in pathological keratinization.

Summary

Measurement of potential and native arginase activities in normal and pathological epidermal tissues showed that psoriatic scales have significantly higher arginase activity than normal stratum corneum and epidermis.

Major differences were found in arginase activity of epidermal tissue from different areas of the body.

An inhibitor of arginase activity, found to be present in normal epidermis, inhibited the abnormally high arginase activity of psoriasis scales.

Human hair roots were found to contain arginase activity.

The possibility that ornithine, resulting from high arginase activity, may take the place of lysine in the keratin molecule in psoriasis was tested. Ornithine was not found in proteins of psoriasis scales.

The relationship of arginase in normal human epidermal tissue to the Krebs-Henseleit ornithine cycle is discussed.

Addendum

Further work has indicated that whereas arginase is inhibited in some specimens of epidermis obtained from surgically removed skin, in other surgical specimens no such inhibition has been found. This apparent discrepancy in results has not yet been explained.

References

1. Kossel, A. & H. D. Dakin. 1904. Über die Arginase. Z. Physiol. Chem. **41**: 321.
2. Mardashev, S. R. & L. A. Semina. 1948. Arginase in the skin. Biokhimiya. **13**: 236.
3. Van Scott, E. J. 1948. Arginase activity in human skin. Science. **113**: 3943.
4. Van Scott, E. J. 1951. Studies on the arginase activity of the skin. J. Invest. Dermatol. **17**: 21.
5. Clementi, A. 1914. Chimica biologica-ricerche sulla arginasi: la distribuzione della arginasi nell'organismo e nella serie dei vertebrati. Atti accad. naz. Lincei. **23**: 612.
6. Hunter, A. & J. A. Dauphinée. 1924. Quantitative studies concerning the distribution of arginase in fishes and other animals. Proc. Roy. Soc. London. **97B**: 229.
7. Baldwin, E. 1935. Arginase. Biol. Rev. **11**: 247.
8. Krebs, H. A. & K. Henseleit. 1932. Untersuchungen über die Harnstoffbildung in Tierkörpern. Z. Physiol. Chem. **210**: 33.
9. Block, R. J. 1935. Basic amino acids of human skin. Proc. Soc. Exptl. Biol. Med. **32**: 1574.
10. Eckstein, H. C. 1935. Amino acids in human skin. Proc. Soc. Exptl. Biol. Med. **32**: 1573.
11. Muting, D., H. Lanhof & V. Wortmann. 1955. Die Aminosäure Zusammensetzung gesunder menschlicher Haut. Z. Klin. Med. **152**: 495.
12. Ward, W. H. & H. P. Lundgren. 1954. The formation, composition and properties of the keratins. *In* Advances in Protein Chem. **9**: 243.
13. Rothberg, S. & E. J. Van Scott. 1958. Evaluation of arginase activity in normal epidermal tissue and pathological stratum corneum. J. Invest. Dermatol. In press.
14. Umbreit, W. W., R. N. Burris & J. F. Stauffer. 1951. Manometric Techniques and Tissue Metabolism. Chap. 1. Burgess. Minneapolis, Minn.
15. Michl, H. 1951. Über Papierionophorese bei Spannungsgefallen von 50 volt/cm. Monatsh. Chem. **82**: 489.
16. Rothberg, S. 1958. Unpublished data.
17. Chinard, F. D. 1952. Estimation of proline and ornithine. J. Biol. Chem. **199**: 91.
18. Harris, H., U. Mittwoch, E. B. Robson & F. L. Warren. 1954. The pattern of amino acid excretion in cystinuria. Ann. Hum. Genetics. London. **19**: 196.
19. Mohamed, M. D. & D. M. Greenberg. 1945. Liver arginase. I. Preparation of extracts of high potency, chemical properties, activation, inhibition, and *p*H optimum. Arch. Biochem. **8**: 349.
20. Rothberg, S. & E. J. Van Scott. 1958. Unpublished data.

PSORIATIC ARTHRITIS

By Alfred Jay Bollet* and Rachel E. Turner

Rheumatic Disease Unit, Department of Medicine, Wayne State University College of Medicine and Receiving Hospital, Detroit, Mich., and Wayne County General Hospital, Eloise, Mich.

There is agreement that arthritis associated with psoriasis, when limited to the distal interphalangeal joints, deserves to be considered a separate entity.[1] The present study is a re-evaluation of the possibility that the more widespread arthritis seen in association with psoriasis should also be considered as distinct from rheumatoid arthritis.

Description of Arthritis Associated with Psoriasis

Our series of 8 patients, although small, illustrates most of the features typically seen in the arthritis associated with psoriasis (TABLE 1). Seven of the 8 were male, with an average age of 46 years. All of the patients were white, although the hospitals in which these cases were studied serve a high proportion of Negro patients.

TABLE 1

CLINICAL FEATURES OF EIGHT CASES OF ARTHRITIS ASSOCIATED WITH PSORIASIS

Age	37 to 58 yr. (average 46)	Arthritis preceded psoriasis	3 cases (3 mo., 2 and 8 yr.)
Sex	7 male 1 female	Psoriasis preceded arthritis	3 cases (10, 13, 21 yr.)
Onset of psoriasis	19 to 54 yr. (average 33)	Distal interphalangeal joint arthritis	6 cases
Onset of arthritis	25 to 46 yr. (average 37)	Hands and feet involved	7 cases
Simultaneous onset of psoriasis and arthritis	2 cases	Nail lesions	6 cases

In each of these patients both arthritis and psoriasis began in adulthood. The earliest age of onset of psoriasis was 19 years; the earliest age of onset of arthritis was 25 years. Arthritis and skin lesions appeared simultaneously in 2 patients. Arthritis appeared first in 3 patients, and psoriasis appeared first in 3. One patient developed a completely disabling arthritis 21 years after the onset of a moderately severe, persistent psoriasis. The more disabling cases of joint involvement seemed to occur in patients with more severe forms of the skin disease. Five of our patients needed prolonged hospitalization for treatment of their skin lesions; several had widespread exfoliation and pustular lesions and 2 developed staphylococcal septicemia.

Simultaneous waxing and waning of the joint and dermatological symptoms have been noted in patients with psoriatic arthritis. In 4 of our patients this phenomenon occurred to some extent; it was difficult to assess in some

* John and Mary R. Markle Scholar in Medical Sciences.

of the others because of the unvarying chronicity of their symptoms, except for the temporary influences of therapeutic measures.

Involvement of the distal interphalangeal joints in psoriatic arthritis has been emphasized. These joints were affected in 6 of the cases included in this report, but in none of these was the disease limited to the distal interphalangeal joints. Other small joints of the hands and feet were affected

FIGURE 1. X ray of hand of patient with psoriasis and arthritis showing cystic areas of bone destruction in the distal end of the ulna and second metacarpal. Narrowing of cartilage spaces in wrist is also evident.

in 7 cases. The arthritis did not extend above the wrists or ankles in 3; proximal large joints were involved in 5 instances. There was arthritis of the cervical spine in 2 cases. Symmetry of the pattern of joint involvement in the extremities, which is often striking in rheumatoid arthritis, was not noted in these patients.

Psoriatic lesions of the nails are another feature frequently reported in psoriatic arthritis; 6 of our patients had these lesions. In 2 there was complete loss of all finger and toe nails.

Clinically, the affected joints in these patients show some inflammatory

changes, including swelling and small effusions, but severe joint inflammation was not observed in any of our patients. Limitation of motion frequently appeared soon after the onset of progressive arthritis, and contractures or severe deformities developed in a few months in 4 cases. In 2 patients, the arthritis began with pain as the sole manifestation, but after 5 years in one instance and 12 years in the other, a rapidly progressive deforming arthritis began. Subluxation of metacarpophalangeal and metatarsophalangeal joints was noted in 5 of our patients.

Pain on motion of the joints was the most striking clinical manifestation of the arthritis in these patients. The pain seemed to correlate with the

FIGURE 2. Bone destruction causing cuplike deformities with invagination of adjacent phalanges of proximal and distal interphalangeal joints of hands.

radiologic evidence of destructive changes within the joint and not with the severity of the inflammation. X rays showed narrowing of the joint space, indicative of cartilage destruction, in involved joints in 6 of the 7 cases for which films were available. The 1 case without changes on X ray had arthritis of only 2 months' duration. Cystic areas of destruction of subcortical bone, although not specific, have frequently been observed in psoriatic arthritis; X rays of 5 of our patients demonstrated this type of lesion (FIGURE 1). Another characteristic of the bone destruction seen in psoriatics is the occurrence of extensive areas of osteolysis, often with complete loss of the original contours of the bone, and marked invagination of one bone into a cuplike deformity in the base of its neighbor. Massive destructive changes of this type were observed in 3 of our cases (FIGURE 2).

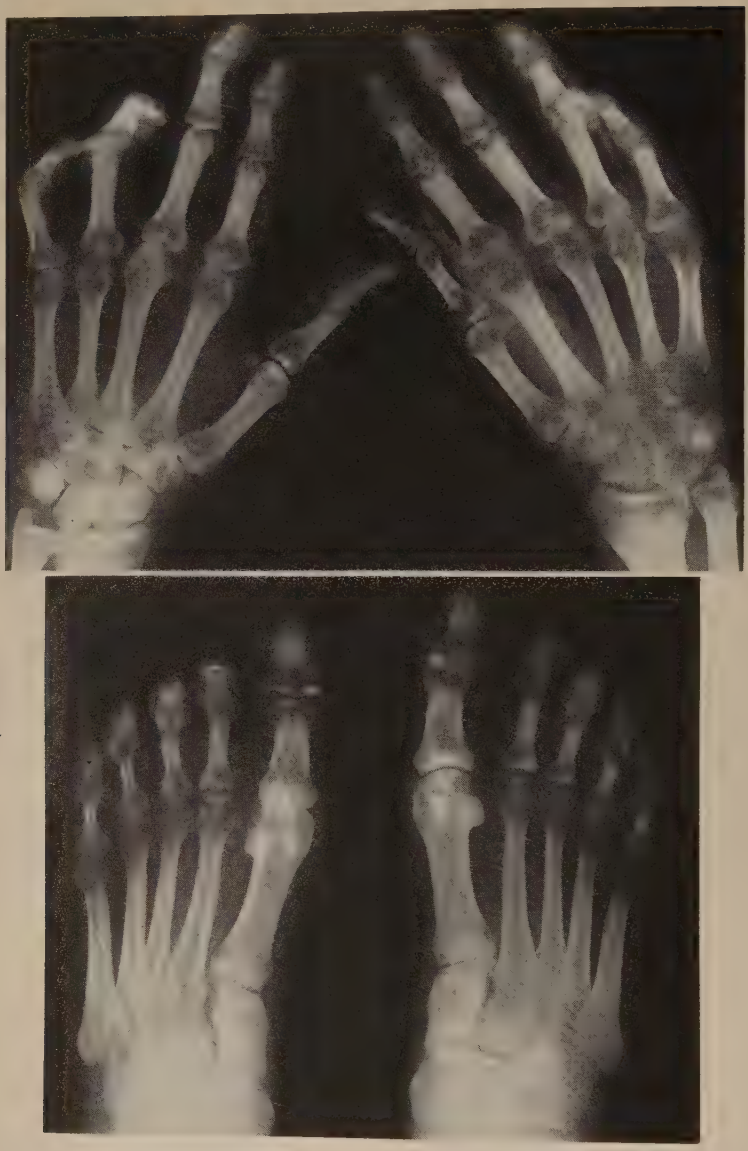

FIGURE 3. Marked osteoporosis of juxta-articular areas of hands (above) and feet (below), showing minimal generalized osteoporosis.

One of our patients demonstrated a unique pattern of osteoporosis. Instead of the generalized osteoporosis with accentuation near involved joints, which is usually seen in rheumatoid arthritis, this patient demonstrated a very marked osteoporosis immediately juxtaposed to all joints of his hands and feet and including distal interphalangeals, with very little thinning of the shafts of the bones in areas between the joints (FIGURE 3).

Table 2

Agglutination Test for Rheumatoid Factor Using Latex Particles

	Number of cases	Positive	% Positive
Rheumatoid arthritis	50	39	78
Psoriasis and arthritis	8	0	0

Among the other laboratory studies made of these patients, two deserve comment. The first is hypochromic anemia, which is frequent in rheumatoid arthritis; such anemia was noted in only 1 of our patients. The second is the agglutination test for rheumatoid arthritis. In our laboratory, using latex particles as the indicator system and diluted test serum plus human gamma globulin (Fraction II) as the reactants,[2] we have obtained positive results in 78 per cent of patients with typical rheumatoid arthritis. None of the 8 patients having psoriasis whom we studied gave a positive test (table 2). This duplicates the experience of other laboratories. Using the most sensitive version of this test, which was devised by Ziff *et al.*,[3] over 99 per cent of patients with rheumatoid arthritis gave positive results, whereas none of the more than 30 psoriatics with arthritis studied have given a positive test.[4]

Relationship to Rheumatoid Arthritis

It is of interest to compare the features of our cases of psoriasis with widespread arthritis to the usual findings in rheumatoid arthritis (table 3).

The preponderance of males in our cases differs from the typical 3:1 preponderance of females among cases of rheumatoid arthritis. The greater incidence of psoriasis and arthritis in males has been noted previously.[5]

The frequency of involvement of the distal interphalangeal joints in psoriatic arthritis would seem to be of significance even when the disease is not limited to these joints, since such involvement is unusual in rheuma-

Table 3

Comparison of Rheumatoid Arthritis and Arthritis Associated with Psoriasis

	Rheumatoid arthritis	Psoriasis and arthritis
Sex incidence	Females > Males	Males > Females
Distal interphalangeal joint involvement	Unusual	Frequent
Symmetrical joint involvement	Frequent	Unusual
Simultaneous changes in skin and joints	—	Frequent
Subcutaneous nodules	21%	None
Massive bone destruction	Unusual	Frequent
Agglutination Test	Positive	Negative

toid arthritis, except for occasional cases of juvenile onset. When these joints are affected in rheumatoid arthritis, it is rare to see the marked destruction and deformities that develop so frequently in psoriatics. In addition, the frequent bilateral symmetry of the joint involvement in rheumatoid arthritis is lacking in the arthritis associated with psoriasis.

The occasional simultaneous onset of skin and joint disease in some cases and the frequent concomitant waxing and waning of skin and joint lesions also suggest a fundamental relationship between these two pathological processes.

Subcutaneous nodules have been reported in 21 per cent of cases of rheumatoid arthritis,[6] but have not been reported in patients with psoriasis and arthritis, and were not found in any of our cases. This may have considerable significance since, microscopically, the subcutaneous nodules of rheumatoid arthritis reveal a characteristic granulomatous process. These granulomata also occur in the synovial membrane in some patients with rheumatoid arthritis. Pathological examinations of joint tissue from patients with psoriasis and arthritis have revealed chronic inflammatory changes, villous hypertrophy, fibrosis, and destructive changes in cartilage and bone.[1, 5] Although similar changes occur in rheumatoid arthritis, the occurrence of these nonspecific lesions in the two states would seem to be of less importance than the failure to find the characteristic rheumatoid granulomata in the tissues of patients with psoriasis and arthritis.

Cartilage and bone destruction occurs in both diseases, and the punched-out cystic lesions and massive osteolysis seen in psoriatics also occur in rheumatoid arthritis, although not as frequently, and usually not with the same speed of development. The marked juxta-articular osteoporosis without generalized osteoporosis seen in one of our cases has not been reported in rheumatoid arthritis.

Synovial fluid studies, including relative viscosity, protein content, cell count,[7] and intrinsic viscosity of hyaluronate,[8] have not revealed any differences in the findings in the two diseases.

Finally, the most important difference between the two diseases seems to be in the agglutination test. Positive results are very frequent in rheumatoid arthritis, but are not found in the arthritis associated with psoriasis, regardless of the clinical characteristics of the arthritis.[4]

Conclusion

Although the arthritis associated with psoriasis, when not limited to the distal interphalangeal joints, shows many of the nonspecific features of rheumatoid arthritis, there are important clinical differences between the two. The lack of specific features of rheumatoid arthritis, such as the absence of the granulomata seen in subcutaneous nodules and the negative test for the rheumatoid agglutinating factor, deserves particular emphasis. Our series, although small, resembles the experience of others.[4, 5] The weight of the evidence seems to favor nosologic classification of psoriatic arthritis as a separate entity.

Acknowledgments

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References

1. Bauer, W., G. A. Bennett & J. W. Zeller. 1941. The pathology of joint lesions in patients with psoriasis and arthritis. Trans. Assoc. Am. Phys. **56**: 349.
2. Singer, J. M. & C. M. Plotz. 1956. The latex fixation test. I. Application to the serologic diagnosis of rheumatoid arthritis. Am. J. Med. **21**: 888.
3. Ziff, M., P. Brown, J. Lospalluto, J. Badin & C. McEwen. 1956. Agglutination and inhibition by serum globulin in the sensitized sheep cell agglutination reaction in rheumatoid arthritis. Am. J. Med. **20**: 500.
4. McEwen, C. 1958. Personal communication.
5. Sherman, M. S. 1952. Psoriatic arthritis; observations on the clinical, roentgenographic, and pathological changes. J. Bone and Joint Surg. **34A**: 831.
6. Short, C. L., W. Bauer & W. E. Reynolds. 1957. Rheumatoid Arthritis. Harvard Univ. Press. Cambridge, Mass.
7. Ropes, M. W. & W. Bauer. 1953. Synovial Fluid Changes in Joint Disease. Harvard Univ. Press. Cambridge, Mass.
8. Sundblad, L. 1953. Studies on hyaluronic acid in synovial fluids. Acta Soc. Med. Upsaliensis. **58**: 113.

THERAPEUTIC APPROACHES IN PSORIASIS

By M. H. Samitz

Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

The treatment of a skin disease may be approached by several means. The following general therapeutic methods have been followed: (1) prophylactic (or preventive); (2) specific; and (3) nonspecific, including (a) oral and parenteral medications, (b) topical therapy, and (c) physical modalities, such as ultraviolet, grenz, and X rays, electrosurgery, and solid carbon dioxide.

(1) *Prophylactic.* Since the etiology of psoriasis is undetermined, there is no prophylactic regimen of proved value. Even though there is definite evidence to indicate hereditary influences and a so-called constitutional background, the suggestion that people with psoriasis or a tendency for psoriasis choose partners free of the psoriatic diathesis would be of little value because the mode of transmission is dominant.

(2) *Specific.* In order to explain this disease, various causal mechanisms have been proposed, such as endocrine, infectious, metabolic, neurogenic, and climatic. There are no conclusive scientific data to indicate that any of these theories have a sound basis. Therefore, therapeutic approaches along these lines will be reviewed under nonspecific therapy.

(3) *Nonspecific therapy.* In psoriasis only nonspecific therapy is available. Evaluation of the true usefulness of nonspecific measures is difficult, because the eruption of psoriasis frequently subsides without any treatment. Therefore, striking results in individual cases with various topical, oral, or parenteral preparations must be accepted with caution. Moreover, most preparations tend to lose effectiveness upon repeated application and administration; recurrences often will not respond to previously successful treatment. Therefore, no therapeutic agent alone or in combination with others will answer the problem of psoriasis.

A brief review of some of the therapeutic agents advocated by proponents of the various presumptive, causal mechanisms follows.

Endocrine. Clinical observations[1] have indicated that the influence of pregnancy in psoriasis seemed beneficial, although adverse effects have also been described. However, no controlled statistical data have been collected. One could postulate that improvement was due to the increase of endogenous estrogenic hormone. With large doses of estrogenic hormones, Kligman[2] recently has noted marked improvement in a small group of patients. In others, however, there was absolutely no effect. The reason for the beneficial effect is unknown; it may be due to an antikeratinizing action, but more probably it is based on interhormonal reactions. Pomerantz and I have followed a small series of psoriatic exfoliative erythrodermas treated with ethynyl estradiol or progesterone. Our results have been equivocal. Continued therapy was not warranted, since these hormones have potential untoward effects.

Adrenocortical steroids occupy an important place in endocrine therapy of psoriasis. We have seen no beneficial effect from the older cortisone and its related newer derivatives. Recently Hollander[3] has reported dramatic results with the use of triamcinolone in cases of psoriasis complicated by arthritis. At one of our conferences Harun[4] reported marked improvement in 60 per cent of a series of 60 patients with psoriasis of varying severity. However, all investigators have noted that after cessation of the steroid therapy the disease invariably recurred and flared up, requiring larger dose schedules of the steroid for control of the disease. Despite the fewer side effects ascribed to triamcinolone, no merit is seen in its indiscriminate use for ordinary psoriasis. Furthermore, the same incidence of improvement, 60 per cent, can be attained by a host of simpler remedies without the ever existent danger attending steroid therapy. The only indication for triamcinolone is severe psoriasis, arthritis, or both in patients in whom the calculated risk of any steroid therapy is justified. The therapeutic effect of the hormone is probably due to its anti-inflammatory action. Steroids also inhibit the formation of ground substance and of collagen fibers.

Infectious. Various antibiotics, sulfonamides, and injections of serobacterins have been reported as efficacious in selected cases of psoriasis. There are no scientific data to indicate a causal infectious agent and these drugs have not been evaluated in controlled studies. In our experience they have no value in routine cases of psoriasis; furthermore, one must caution against the promiscuous prescribing of antibiotics and chemotherapeutic agents. The use of sulfanilamide to induce photosensitivity and thereby enhance topical tar applications is a dangerous measure. The concept of a bacterial-allergic chain reaction due to a bacteremia of the *B. endoparasiticus* Benedek and treatment with specific vaccine therapy as advocated by Benedek[5] lacks verification. Treatment with suspensions or extracts of psoriatic scales has given such variable results as to be not dependable and of no proved value.

Metabolic. The concept of a metabolic disturbance as the cause of psoriasis has resulted in a deluge of diets and vitamins, which have proved disappointing.

After developing a theory of disturbed nitrogen metabolism in psoriasis, Schamberg[6] suggested a low protein diet for treating this disease. The theory lacks laboratory and clinical verification.[7] Gruetz and Burger[8] focused attention on the possibility that psoriasis was a disturbance of lipid metabolism. It seems that psoriasis has been reported as less common after the two world wars. This phenomenon was explained on the ground that the people in the areas of strife were on lipid-poor diets. Low-fat diets were therefore advocated for psoriasis. When these proved ineffective, various adjuvants were supplemented to correct disturbances in fat metabolism. A cholesterol disturbance and a deficiency of pancreatic enzymes were implied, but never proved. Lipotropic factors such as lipocaic,[9] soybean lecithin,[10] sarsaparilla,[11] phospholipids, and bile salts have been promoted. To show that this type of therapy is not the answer to the problem, one need only quote Gross and Kesten,[10] who based their observations on a

10-year clinical study: "The complete failure of this therapy in 37 out of 155 cases intensively treated and carefully followed must lead to the conclusion that this form of therapy is capable of correcting some of the metabolic defects but not the actual cause of the disease." In evaluating pancreatic extracts in the treatment of psoriasis, Farber and Schneider[12] showed in a controlled clinical study that improvement with pancreatic extracts was no greater than the improvement obtained with placebos. One can only conclude that the use of lipotropic substances is an expensive form of therapy of no proved value.

Proponents of vitamin therapy are also numerous. Unfortunately, no vitamin seems to solve the problem. In the wake of vitamin D and viosterol,[13, 14] exploited and disproved in the late thirties, came vitamin B and its various factors, lemon citrin (vitamin P) and ascorbic acid, and vitamin A. Vitamin A contributed a most confusing picture. Some investigators claimed that its virtue was due to its antikeratinizing action. Another group[15] reported good results with restricted intake of carotene and vitamin A. Their reasoning was based on the following: (1) psoriasis is a disease of defective keratinization, histologically characterized by parakeratosis, and (2) vitamin A deficiency produced a keratoplasia. The latest additions to the vitamin shelf for psoriasis are riboflavin and B_{12}. In an appraisal of the therapeutic effect of riboflavin in psoriasis by Welsh and Ede[16] no significant response was reported. It is also difficult to explain the possible mechanism of vitamin B_{12}. It seems incongruous that vitamin B_{12}, which is essential for maturation of epithelial cells, has been advocated at the same time that Aminopterin, a folic acid antagonist, has proved helpful in the same disease process. Personal experiences with vitamins gave no conclusive evidence of the efficacy of any vitamin singly or in combination.

Neurogenic. Tension, anxiety, and an emotional overlay can play a role in many disease processes. Undoubtedly, the psoriatic is also influenced by emotional factors, and the visible effects of psychic disturbances are readily noticeable. There is no substantial evidence that functional disorders play a role in the causation of psoriasis, nor can the amelioration of the patient's tension and anxiety be the answer to the problem. However, our present tranquilizing era has invited the use of ataractics. Uncontrolled studies have reported favorable results with chlorpromazine[17] and *Rauwolfia* extracts[18] in selected cases of psoriasis.

Climatic. There is clinical evidence to indicate that psoriatics improve during the summer and in warm, sunny climates. However, it is also evident that psoriasis attacks many individuals living in warm environments and some psoriatics are aggravated by sunshine. It is therefore unreasonable to expect the solution of the problem from this factor. It is possible that pigment cells play a role, as indicated both by the rarity of psoriasis in the Negro and by pigment changes in association with the involution of psoriasis.

As long as the etiology of psoriasis remains obscure and specific therapy is unavailable, the treatment of the disease should be directed against an abnormal reactive skin, altered in its epidermal metabolism. Since we have definite data on the histopathological changes and on some biochemical

alterations in the psoriatic skin, a more rational therapeutic approach may develop along these lines. Measures to correct the alterations in the epidermis and corium and the manner in which they influence the pathological and biochemical changes are reviewed below. These measures include external applications and internal medications.

External measures. Because of our present limited knowledge, topical treatment constitutes the most important part of therapy for psoriasis. The main objectives of topical applications are to modify the epidermis or the corium, or both.

Many such agents have been advocated, but of these only a relatively small number warrant consideration: mercury, salicylic acid, resorcinol, allantoin, sulfur, detergents, chrysarobin and anthralin, tar and related compounds, and podophyllin.

Mercury may influence the process of keratinization by reacting with SH-groups. After discontinuation of topical mercury therapy, SH- groups are absent for weeks from the horny layer. Absorption of mercuric ions from ammoniated mercury is a slow and probably steady process.

Salicylic acid, resorcinol, and all phenolic compounds attack hydrogen bonds in the horny layer and epidermis. This results in keratin dispersion and frequent disaggregation of epidermal cytoplasm (retecytolysis).

Allantoin is a urea derivative and, like urea, it disperses keratin by attacking hydrogen bonds.

Sulfur may become incorporated in the keratin molecule. A recent study[19] using radioactive sulfur in psoriatic skin suggests that sulfur is involved in an intracellular sulfhydryl-containing enzyme system. The effect of sulfur on psoriasis is probably dependent upon its keratolytic and keratoplastic properties.

Detergents may break up the horny layer by extracting intercellular cementing matrix and by removing both the lipids around the water-soluble compounds and the water-soluble components themselves.

The mode of action of tar is unknown. It contains phenolic compounds that break up the horny layer and it also sensitizes toward ultraviolet, an action utilized in the Goeckerman regimen.

Podophyllin has a cytotoxic action affecting mitotic activity. The basal layer, which is most active metabolically, is the most susceptible to the drug action.

Most of these chemical agents have been in use for many years and have proved their clinical effectiveness. We carried out clinical studies with some of the newer drugs. Podophyllin, in concentrations ranging from 2 to 25 per cent, was used on inveterate psoriatic plaques. At times the pruritus associated with these lesions was lessened; however, the psoriasis more often remained unchanged rather than improved. Pomerantz and I carried out a clinical study with an allantoin* preparation and noted a very marked improvement in 30 per cent of a group of 30 patients resistant to previous therapy.[20] In this study, controls were used by anointing one side of the body or one extremity with the preparation's vehicle. We have also

* Alphosyl was supplied for this study by Reed and Carnrick, Jersey City, N. J.

found that the use of hydration baths in the aftertreatment of the dry skin is a valuable adjunct to topical therapy. Water replacement helps to correct the decreased water-holding capacity of the psoriatic horny layer. The procedure relieves dryness and improves the skin's flexibility. In a clinical evaluation of various ointment bases for the hydration routine, we have found that an ointment base* especially prepared for this purpose was non-irritating and most satisfactory.

Irradiations with ultraviolet, grenz, and X rays are commonly used external measures in the treatment of psoriasis. The modes of action of the various rays on the epidermis and corium are not well known. Irradiation with ultraviolet light has a limited range of value. The combination of tar and ultraviolet recommended by Goeckerman and O'Leary[21] has often proved exceedingly effective, however. Clinical evidence of the temporary merits and limitations in the use of X rays and the potential dangers in association with these ionizing rays has been well established and needs no further elaboration in this discussion.

Internal measures. Some of these have already been reviewed in the discussion of the endocrine, infectious, metabolic, and neurogenic mechanisms. The mode of action of various hormones and vitamins has been noted. Vitamin B_{12}, however, deserves further elaboration. It is concerned in the maintenance of sulfhydryl enzyme systems. The vitamin favors the reduction of SS- groups and retards the oxidation of SH- groups, yet histochemical changes in psoriasis show a sulfhydryl increase. It would seem that the opposite action (vitamin B_{12} deficiency characterized by a reduction in SH-content) would be more appropriate in psoriasis.

Of the older internal drugs used for psoriasis, inorganic arsenic and iodides have been tried. Iodides may act on the inflammatory process in the corium and play a role by promoting absorption. Arsenic has an unknown effect. It may act through vasodilation; arsenic also combines with sulfhydryl groups, "solidifies" keratin, and stimulates keratin formation. Prolonged use of arsenic in some individuals, however, causes an abnormal proliferation of epithelium leading to keratosis or multiple epidermal carcinoma. Its use is therefore a potentially dangerous measure.

Oral administration of undecylenic acid was suggested by Perlman.[22] Little is known about the fundamental mechanisms of action of fatty acids. A desquamating action was observed. Administration of the drug was often associated with disagreeable side effects. A small percentage of patients was reported to obtain benefit from therapy. Since controlled studies by competent investigators failed to support these claims, this form of therapy in the management of psoriasis was considered useless.

In 1949 Klinck[23] reported encouraging results with gamma globulin in the treatment of six patients with psoriasis. No studies were made to estimate gamma globulin values in the blood of any of the patients before, during, or after treatment. No theory was advanced to explain the mode of action of gamma globulin other than the possibility that psoriasis was influenced by the level of antibodies in an individual. Pomerantz and I[24]

* Supplied for this study by Martin-Valer, New York, N. Y.

carried out a study to evaluate the efficacy of gamma globulin in the treatment of severe forms of psoriasis. This study also afforded an opportunity to determine the electrophoretic patterns in 5 selected cases and to observe pattern changes during treatment. Four patients had psoriatic exfoliative erythroderma of from 1 to 3 years' duration. One patient had severe generalized psoriasis, recalcitrant for many years to all previous forms of therapy. Electrophoretic patterns were obtained before and during treatment. Gamma globulin* in 10 cc. doses was administered intramuscularly at weekly intervals. None of the patients showed any improvement in their psoriasis. No significant changes in the electrophoretic patterns were noted throughout the 12 weeks of observation.

Recently Aminopterin, a folic acid analogue, has been introduced in the treatment of psoriasis.[25] Aminopterin (4-amino pteroylglutamic acid) interferes with the conversion of folic acid to citrovorum factor; without this factor epithelial cells cannot develop. Studies by Rees *et al.*[26] with Aminopterin in psoriasis showed an inhibition of cell proliferation and reduction of hyperkeratosis, parakeratosis, and acanthosis. Aminopterin is a potentially dangerous drug, although the lower dosage schedule recommended by the foregoing investigators showed no noticeable serious side effects. This type of therapy should be restricted to patients with extensive involvement and to those who have failed to respond to the ordinary forms of treatment. The use of Aminopterin in the routine management of psoriasis is not warranted.†

Pomerantz and I[27] made therapeutic trials on a selected group of 5 psoriatic erythrodermas with small doses of nitrogen mustard—5 mg. intravenously—followed by the oral administration of a low dosage course of Leukeran‡ (chlorambucil, a nitrogen mustard derivative) on a selected group of 5 psoriatic exfoliative erythrodermas. A striking improvement was noted in 1 patient and distinct improvement in a second. Complete clearing of the psoriasis, however, was not achieved. No ill effects were noted. Except for temporary leukopenia in 1 patient, complete blood counts showed no significant changes. Further experience in a larger series of patients is necessary before conclusions can be drawn as to the value of these drugs in the management of the more severe forms of psoriasis. Like Aminopterin, nitrogen mustard products are not justified in the treatment of ordinary psoriasis.

* Gamma globulin for this study was supplied by Lederle Medical Research Dept., American Cyanamid Co., Pearl River, N. Y.

† The following quotation from a recent study provides additional information: "Aminopterin was administered to 348 individuals with psoriasis according to schedules used in the previous study. Approximately 45 per cent of these patients noted 75–100 per cent clearing of their lesions, and another 19 per cent, approximately, had 50–75 per cent clearing. This makes a total of 64 per cent having enough benefit to make the treatment seem worth while. The overall incidence of toxicity was found to be between 15 and 20 per cent, although patients having an excellent response had an incidence of reactions of about 27 per cent. This substantiates the view that benefit is brought about largely by toxic effect."[28]

‡ Leukeran was supplied by Burroughs Wellcome Co. (U. S. A.) Inc., Tuckahoe, N. Y.

In our experience, there is little need of systemic medication for ordinary psoriasis. Control of the psoriatic eruption is obtained by suitable topical regimens which include such measures as hydration baths, tar-ultraviolet combinations, and externally applied medications fitted to the requirement of the individual patient. However, the management of severe extensive psoriasis, pustular psoriasis, and psoriasis in association with arthritis at times remains a problem.

Summary

There are no definite prophylactic measures that can be instituted to prevent the development of psoriasis.

The etiology of psoriasis is as yet unknown and all forms of treatment are empirical. Endocrine, infectious, metabolic, and neurogenic factors have been considered. However, there are no conclusive scientific data to confirm the efficacy of hormone therapy, fat-free and low-cholesterol diets, vitamins, or anti-infective agents. Despite the few complications ascribed to triamcinolone, no merit is seen in its use for ordinary psoriasis. This compound shows promise in managing patients who have psoriasis, arthritis, or both, in sufficiently severe form to justify the calculated risk of any steroid therapy. Evaluation of any of these therapeutic regimens is difficult, because the disease process tends to fluctuate and may involute spontaneously.

Hosts of topical preparations have been advanced for local therapy. The fact that there are so many speaks eloquently for their inadequacy. Evaluation of any preparation is insufficient without control studies; moreover, all preparations tend to lose effectiveness upon repeated application. The use of irradiation (ultraviolet, grenz, and X rays) has been advocated; however, the indiscriminate use of X rays is dangerous.

Our present limited understanding of the pathogenesis of psoriasis precludes a cure until such knowledge is available. Meanwhile, a rational therapeutic approach should utilize measures to correct the known altered epidermal metabolism. These measures include external and internal medications. The selection of the therapeutic measures must be skillful and fitted to the requirements of the individual patient. As a rule, in the routine management of psoriasis, such measures as hydration baths, tar-ultraviolet combinations, and suitable externally applied preparations prove exceedingly effective.

Topical preparations, internal medications, and the manner in which they influence pathological and biochemical changes have been reviewed. Among the newer topical preparations an allantoin lotion was tested on the basis of the keratin-dispersing ability of allantoin and was found beneficial in many patients resistant to previous therapy. Aminopterin, on the basis of inhibiting epithelial proliferation, has been reported as an effective measure in psoriasis, but severe side-effects preclude its use in the ordinary case.

Full knowledge, however, is still lacking and the cure of psoriasis remains a problem.

References

1. LeWinn, E. B. & I. Zugerman. 1941. Fat tolerance tests in psoriasis. Am. J. Med. Sci. **201**: 703.
2. Kligman, A. 1958. Personal communication.
3. Hollander, J. 1958. New drug for skin lesions described. Phila. Med. **54**: 6.
4. Harun, J. S. 1958. Treatment of psoriasis with triamcinolone. Treatment of Psoriasis and Other Dermatoses with Triamcinolone. Univ. Pa. Dermatological Conf. Philadelphia, Pa. In press.
5. Benedek, T. 1955. Psoriasis and its specific vaccine therapy. Acta Dermato-Venereol. **35**: 33.
6. Schamberg, J. F. 1932. Dietary treatment of psoriasis. J. Am. Med. Assoc. **98**: 1633.
7. Block, W. D., W. A. Lea, Jr., A. C. Curtis & E. F. Cannon. 1957. Nitrogen balance studies in psoriasis. 18th Ann. Meeting Soc. Invest. Dermatol. New York, N. Y.
8. Gruetz, O. & M. Burger. 1933. Die Psoriasis als Stoffwechselproblem. Klin. Wochschr. **12**: 373.
9. Clark, D. E., L. R. Dragstedt & S. W. Becker. 1941. Further observations on the use of lipocaic in the treatment of psoriasis. J. Invest. Dermatol. **4**: 59.
10. Gross, P. & B. M. Kesten. 1950. The treatment of psoriasis as a disturbance of lipid metabolism. N. Y. State J. Med. **50**: 22.
11. Thurman, F. M. 1942. The treatment of psoriasis with a sarsaparilla compound. New Engl. J. Med. **227**: 4.
12. Farber, E. M. & H. M. Schneider. 1957. Pancreatic extracts in treatment of psoriasis. A.M.A. Arch. Dermatol. **76**: 2.
13. Cedar, E. T. & L. Zon. 1937. Treatment of psoriasis with massive doses of crystallin vitamin D and irradiated ergosterol; preliminary report. Public Health Repts. U. S. **52**: 1580.
14. Madden, J. F. 1940. Treatment of psoriasis. J. Am. Med. Assoc. **115**: 588.
15. Hoffman, R., E. J. Lorenzen & A. S. Garfinkle. 1947. Effects of restricted intake of carotene and vitamin A on psoriasis vulgaris. New Engl. J. Med. **236**: 25.
16. Welsh, A. L. & M. Ede. 1957. An appraisal of the therapeutic effect of riboflavin in psoriasis. A.M.A. Arch. Dermatol. **76**: 5.
17. Fisher, R. A. & J. L. D'Silva. 1956. Chlorpromazine in the management of psoriasis. Ill. Med. J. **110**: 3.
18. Wrong, N. M. & E. D. Caldbick. 1956. Treatment of psoriasis and other chronic dermatoses with extracts of *Rauwolfia serpentina*. Can. Med. J. **74**: 10.
19. Scott, A. 1957. The behavior of radioactive sulfur after its external application to the skin. Brit. J. Dermatol. **69**: 2.
20. Samitz, M. H. & H. Pomerantz. 1958. Unpublished data.
21. Goeckerman, W. H. & P. A. O'Leary. 1932. Erythroderma psoriaticum. J. Am. Med. Assoc. **99**: 2102.
22. Perlman, H. H. 1949. Undecylenic acid given orally in psoriasis and neurodermatitis. J. Am. Med. Assoc. **140**: 865–868.
23. Klinck, G. H., Jr. 1949. Reaction of psoriasis following use of gamma globulin J. Invest. Dermatol. **12**: 5.
24. Samitz, M. H. & H. Pomerantz. 1957. In press.
25. Gubner, R. 1951. Effect of Aminopterin on epithelial tissues. Arch. Dermatol. and Syphilol. **64**: 688.
26. Rees, R. B., J. H. Bennett & W. L. Bostick. 1955. Aminopterin for psoriasis. A.M.A. Arch. Dermatol. **72**: 2.
27. Samitz, M. H. & H. Pomerantz. 1957. Unpublished report.
28. Rees, B. R. & J. H. Bennett. 1958. Further observations on Aminopterin for psoriasis. 19th Ann. Meeting Soc. Invest. Dermatol. San Francisco, Calif.

CLINICAL EXPERIENCE WITH A NEW PREPARATION FOR THE TREATMENT OF PSORIASIS

By Jacob Bleiberg
Beth Israel Hospital, Newark, N. J.

The observations and conclusions presented in this report are based on experience with a consecutive series of psoriatic patients seen in a private dermatological practice. In all but one instance, the patients presented a psoriasis resistant to all previous therapeutic measures and of many years' duration.

There is little doubt of the existence of a psychic component in the response of the psoriatic patient to therapy as well as in the flare-ups of the disease. It has been said that where the unenthusiastic physician might expect a 50 or 60 per cent response to therapy, the enthusiastic physician may be able to obtain a 90 per cent response to the same medication. However, the remissions observed, as a result of either new therapy or confidence in a new physician, are not of an enduring nature.

In any study of psoriasis it is advisable to establish treatment controls of any observed results obtained with a new therapy. Such controls of clinical observations were obtained in our study in two different ways. First, since all but one patient had a psoriasis of long duration and resistant to all previous therapy, the patient served as his own control. In this series the psoriatic "rhythm" of many of the patients was known from clinical observation over the years. We could predict periods of remission and exacerbation with reasonable accuracy. In other patients the lesions showed little variation during the course of the year or, indeed, over many years. Therefore, on the basis of clinical experience, the observed response in these patients could be attributed to the medication.

The second control was obtained through observation of those patients in whom a remission was achieved with the medication, followed by a reappearance of lesions on cessation of therapy. In these patients the relapse cleared promptly on reapplication of the medicament.

It should be noted also that the time selected for initiating this investigation was at the advent of fall and winter. This minimizes the likelihood of benefit from seasonal factors, since at this time most cases tend to become aggravated. We attempted also to be extremely careful of the factors of psyche and attitude, and great care was exercised to avoid giving the impression that the patient was being given a new miracle drug.

Diagnostic Features

In the majority of cases psoriasis is easy to diagnose; the lay patient often furnishes his own correct diagnosis. Some types, however, are extremely difficult to diagnose. Psoriasis of the penis presents an almost impossible situation, even with the aid of biopsy. Identification of psoriasis of the hands, and of the face, where lupuslike coverage occurs, is also difficult.

Sometimes the lesions strongly resemble seborrheic dermatitis; these have been designated as "sebsor."

In these difficult cases we looked for other areas of characteristic psoriatic involvement; since these are nearly always present, the nature of the atypical lesion can be established. An unusual case, in which a clue was furnished by a chain of symptoms, is of interest. This patient presented advanced ptyalism, and laboratory findings indicated severe kidney damage. In considering the possibility of mercury poisoning, with the thought of heavy exposure to ammoniated mercury, we questioned the patient about skin lesions. It developed that she had been treated for thirty years with ammoniated mercury for her psoriasis.

Material and Method of Study

The medication used in this study is a new lotion (Alphosyl) containing allantoin (2 per cent) and coal tar extract (5 per cent).* This was massaged into the lesions two to four times daily. Where the lesions were of the hard, crusty variety, a hot bath was advised prior to application of the lotion. In some instances it was necessary to remove as much of the scale as possible by mechanical means before applying the medication.

Once scaling was under control, and induration and erythema diminished, it was often possible to reduce the number of applications to one or two daily. A further reduction to a single application daily or every few days was made where complete clearing was achieved. In each case the frequency of maintenance therapy was determined by experience, the criterion being prevention of regression. Persistence in continuing on the maintenance regime was emphasized, the alternative being recurrence of the disorder, with consequent reinstitution of the therapeutic schedule of applications. Patients were asked in particular to compare the results against those obtained with medications they had used previously. In addition, clinical evaluation of the response was made. These evaluations were graded as completely cleared; greatly improved (all areas cleared except for a few resistant areas, usually on the elbows or knees); moderately improved (at least 50 per cent improvement in the appearance of lesions); and slightly improved (at least 25 per cent improvement in the appearance of lesions). A lesser degree of improvement would be classified as a failure for the medication.

More than 50 patients were treated with the allantoin-tar lotion. A number of these could not be followed up; hence useful data are available on only 42 of the cases.

Results

Questioning of the patients revealed an almost uniform satisfaction with the preparation. None felt that he had derived more benefit from previous medication, although three commented that other preparations had been equally effective. The majority were enthusiastic about the lotion and adjudged it superior. It was especially well received as cosmetically superior

* The allantoin-tar lotion (Alphosyl) used in this study was supplied by Reed & Carnrick, Jersey City, N. J.

to other medication. A few patients mentioned the slight tarry odor, but this did not affect acceptance.

Objective clinical evaluation of the results disclosed a rate and degree of response unequaled by any medication in our previous experience. In general, early lesions responded more quickly than old, chronic lesions; however, there was no clear correlation between the type or age of lesion and the rate or magnitude of response. An interesting exception to this is psoriasis of the scalp. Results in this disorder were striking; of 16 cases treated, 13 showed complete clearing, and the remaining 3 were greatly improved.

We have had a chronic case of psoriasis of the scalp and the elbow, with severe scaling and shedding. The patient telephoned after 3 days of therapy to report complete clearing. Also, we had a case of generalized ostraceous psoriasis of 10 years' duration that cleared completely in 5 weeks. On the other hand, apparently similar cases showed only marked improvement after as much as 16 weeks of therapy. The over-all results are summarized in TABLE 1.

TABLE 1
RESULTS OF TREATMENT WITH ALLANTOIN-TAR LOTION

Response	No. of cases
Completely cleared	19
Greatly improved	15
Moderately improved	3
Slightly improved	3
No improvement	2
Total	42

With one exception, all patients were chronic sufferers who had proved resistant to other therapy or had relapsed while still on their previous medication. In due course, all patients do respond to the medication, at least to some degree; they do not become resistant to it, nor do they "rebound" while on therapy. In fact, when relapses occurred we could extract the admission that the patient was careless about applying the medication.

Of the two patients classed as failures, there is serious doubt about use of the medication in one; the other is a severe arthritic with generalized exfoliative psoriasis who has been on steroid therapy since 1950 and who developed a typical Cushing syndrome. This latter patient claimed that the lotion caused irritation.

Discussion

In a previous preliminary report that included some of the cases reported above, Bleiberg and Saltzman[1] described marked benefit in approximately 60 per cent of cases, as compared to about 80 per cent in the present report. Some patients included in the earlier study have shown additional progress with continued treatment. Also, as we progressed with our study it became

apparent that greater attention to scale removal was required in certain instances. This factor, together with such modifications in dosage schedules as were indicated by experience, accounts for the improved results.

When our attention was first directed to this preparation, the literature on allantoin was reviewed; its properties indicated that its inclusion in a topical medication for psoriasis offered attractive prospects. Recent studies on the chemistry of psoriatic scales and the manner in which scale is affected by the action of allantoin[2] shed new light on therapy. It appears that some types of scale are not affected materially by allantoin, while in other types allantoin exhibits a keratin-dispersing action. It is logical to expect, therefore, that the degree of benefit observed in any patient is related to the susceptibility of the scales of that patient to dispersal by allantoin.

Summary

Forty-two patients with chronic psoriasis resistant to previous therapy were treated with a new lotion (Alphosyl) containing allantoin and coal tar extract. Complete clearing of lesions was observed in 19 of the patients, and marked improvement was observed in 15 more cases. Prolonged treatment was required in some instances. Treatment-fastness did not occur. The preparation is well tolerated and cosmetically most acceptable.

References

1. Bleiberg, J. & J. A. Saltzman. 1958. Experience with a new preparation in the local treatment of psoriasis: a preliminary report. Clin. Med. **5.**
2. Flesch, P. Personal communication.

CLINICAL EXPERIENCE WITH A NEW PREPARATION FOR THE TREATMENT OF PSORIASIS: A PAIRED COMPARATIVE STUDY*

By Sidney G. Clyman
Mount Vernon, N. Y.

In conducting a study for the treatment of psoriasis, one of the most challenging problems is the attitude of the patient. The typical chronically affected patient is an unhappy, annoyed, frustrated individual. Because many commonly used medicaments are greasy, messy, and onerous, treatment is frequently neglected. The plight of those afflicted is such that any new medication is embraced with bated anticipation provided the reported results and physicians' interest appear genuine. In some the benefit derived from the new medication may be attributed, in part, to psychic factors and the physician's attitude. It is also likely that the patient will follow the new regimen more conscientiously and will, therefore, often secure a superior result as a consequence of fidelity to the new therapeutic regimen.

In assessing the efficacy of a new topical preparation, it is necessary therefore to adopt a procedure of clinical evaluation that equalizes all influences except those due solely to the medication. For our purposes we adopted the "symmetrical paired comparison" technique described by Sulzberger, Baer, Kanof, and Lowenberg[1] and by myself[2] in a previous report.

It must be stated at the outset that, strictly speaking, true comparisons between different topical agents are difficult to achieve. For example, in this study I compared responses observed after application of a lotion to those obtained with the use of a greasy ointment. Apart from the influence of the vehicle itself on the effectiveness of topical medication, there enters into the picture of practical therapy the willingness of the patient to use the medication as a matter of esthetics.

The dosage regimens for the two test preparations were different. By clinical experience it was determined that the usual and useful frequency of application in the case of the ointment was two applications daily and three for the lotion. In our study, therefore, we compared the two preparations at their corresponding application frequencies. The cosmetic advantages of the lotion made it quite acceptable for thrice daily application.

Plan of Study

The materials used for comparison were: (1) an ointment containing ammoniated mercury 5 per cent, acid salicylic 3 per cent, and liquor carbonis detergens 5 per cent, a preparation that I have used for some time and that has proved as effective in psoriasis as any preparation I have studied

* The work described in this paper was done in treating private patients in Mount Vernon, N. Y.

to date; and (2) the test lotion,* which contains allantoin 2 per cent, and refined coal tar extract 5 per cent, in a vanishing-type base.

Patients were instructed to apply the ointment to lesions on one side, and the lotion to lesions on the contralateral side. Where extremities were involved, this proved easy to explain. When the lesions were on the trunk and the face, especially where they were confluent, it was necessary to draw an imaginary line of demarcation for the applications. Naturally, consistency in adhering to the routine was emphasized.

Thirty-nine psoriatic patients were treated in this paired comparison study. The patients range in age from 8 to 57 years. In general, the ointment was used for a period of 3 weeks only, because of either of 2 events. Either no improvement was noted with either therapy and the patient discontinued it, or little improvement was noted with the ointment and marked improvement with the lotion, and the patient requested permission to use the lotion on all lesions. In some cases, because of irritation by the ointment, petroleum jelly was substituted. Eight of the patients received supplemental grenz ray therapy when the response to medication was unsatisfactory. In one case, folliculitis appeared during the course of therapy with the lotion; this cleared up on topical antibiotic therapy.

It is necessary to introduce one note on the method of application. During the early stages of our study, the slowness of response in some cases led us to inquire into the method of use of the medication. It was particularly true of the lotion that, because of its ease and smoothness of application and its vanishing character, many patients were disposed to apply it lightly with either a cotton pledget or the fingertips. These patients were directed to massage the lotion into the lesion more energetically, with better subsequent results.

Criteria of Response

Rather than attempt to evaluate improvement by percentage estimations, we used a method of assessment describing the response to therapy. Thus, as indicated in the table, a zero indicates no change; one-plus indicates removal of scales; two-plus, removal of scales with a decrease in erythema; and three-plus, complete clearing (TABLE 1).

The two-plus response alone requires elaboration. The designation "decrease in erythema" may, of course, be applied to a reduction in redness ranging in degree from slight to almost complete. For the sake of simplicity, all gradations are included in this single category.

In only one instance (case 4) did the lesions become worse, and that occurred in the area treated with the mercury-salicylic acid-tar ointment.

Findings

The studies were useful in furnishing an indication of the comparative effectiveness of a standard psoriasis ointment and the new lotion preparation.

Examination of the results observed after three weeks (TABLE 1) reveals

* The allantoin-tar (Alphosyl) lotion used for these studies was furnished by Reed & Carnrick, Jersey City, N. J.

TABLE 1
PAIRED COMPARATIVE STUDY USING ALPHOSYL LOTION AND A STANDARD OINTMENT

Case				Results					
				1 week		3 weeks		6 weeks	
No.	Initials	Age	Diagnosis	Oint. (1)	Tar-allantoin lotion (2)	Oint. (1)	Tar-allantoin lotion (2)	Tar-allantoin lotion (2)	Tar-allantoin lotion (2)
1	LM	26	Patches elbows, knees, trunk	+	+	+	++	++	++
2	BB	42	Patches elbows, knees, trunk	+	+	+	++	++	++
3	CA	8	Patches extremities, trunk	+	++	+	+++	+++	+++
4	IM	29	Patches extremities, trunk	*	++	+	+++	+++	+++
5	JC	31	Patches extremities, trunk	+	++	++	+++	++	++
6	RL	17	Patches extremities, trunk	++	+	++	++	++	++
7	JV	45	Patches extremities, trunk	+	+	+	++	++	++
8	AD	55	Patches extremities, trunk	+	+	+	++	++	++
9	IR	10	Patches extremities, trunk	+	++	+	++	++	++
10	CR	8	Pustular psoriasis of soles	0	+	−	++	+++	+++
11	YB	52	Pustular psoriasis of soles	0	0	0	+	+	+
12	NN	40	Pustular psoriasis of soles	+	+	+	+	Oint. (1) +	0
13	OY	25	Pustular psoriasis of soles	0	+	0	+++	+++	+++
14	SL	21	Patches, trunk, arms	+	++	+	+++	++	++
15	AP	54	Patches, trunk, extremities, confluent and widespread	+	++	+	++	++	++
16	AM	45	Generalized psoriasis	Pet. +	+	+	++	++	++
17	TN	33	Patches, trunk, extremities	+	+	+	+	Oint. (1) +	0
18	WK	15	Patches, trunk, extremities	0	+	+	++	+++	+++
19	HO	39	Patches, trunk, extremities	+	+	+	++	++	++
20	LH	52	Patches, trunk, extremities	+	0	+	0	−	−

TABLE 1 (*Continued*)

Case				Results					
				1 week		3 weeks		6 weeks	
No.	Initials	Age	Diagnosis	Oint. (1)	Tar-allan-toin lotion (2)	Oint. (1)	Tar-allan-toin lotion (2)	Tar-allantoin lotion (2)	Tar-allan-toin lotion (2)
21	TB	24	Patches, trunk, extremities	+	0	+	0	Oint. (1) Grenz +	++
22	HR	29	Patches, trunk, extremities	+	+	+	+	++ Grenz	++
23	HA	15	Patches, trunk, extremities	0	+	Pet. ++	+		
24	FL	30	Patches, trunk, extremities	+	0	++	0		
25	GW	33	Patches, trunk, extremities	++	0	++	0		
26	MN	25	Patches, trunk	++	0	+++	0		
27	PK	24	Patches, buttocks, sacrum	0	0	0	0	0 Grenz	0
28	RJ	36	Thick patches, knees	0	0	0	0	+	+
29	FK	23	Thick patches, knees	0	0	+	0	+ Grenz	++
30	DB	32	Thick patches, knees, arms	0	0	+	0	+	++
31	RM	29	Inguinal psoriasis	Pet. 0	0	0	0		
32	SC	28	Inguinal psoriasis	Pet. 0	0	0	++	++ Grenz	++
33	PR	41	Inguinal psoriasis	Pet. 0	+	+	++	++	++
34	BS	57	Patches, trunk, extremities	+	0	+	0		
35	AC	51	Patches, trunk, extremities	0	0	0	0		
36	LMcD	30	Patches, trunk, extremities	+	+	+	+	Oint. (1) ++ Grenz	+++
37	NG	20	Patches, trunk, extremities	+	+	+	+	Oint. (1) + Grenz	++
38	SM	18	Patches, trunk, extremities	0	0	+	+	Oint. (1) + Grenz	++
39	LR	24	Patches, trunk, extremities	0	0	0	0		

Legends: Oint. (1) = ointment of ammoniated mercury 5%, acid salicylic 3%, liquor carbonis detergens 5%; tar-allantoin lotion (2) = lotion containing allantoin 2%, coal tar extract 5% (Alphosyl); Pet. = petrolatum.

Key to responses: +++ = complete clearing; ++ = scales off and decrease in erythema; + = scales off; 0 = no response; * = worse.

that substantial benefit (two-plus and three-plus responses) was observed in twenty-five of the patients receiving applications of the new lotion, as against only six of the patients on ointment therapy. Complete clearing occurred in six patients on the lotion as against one on the ointment.

As mentioned previously, after 3 weeks the majority of patients requested permission to use the lotion on the contralateral sides rather than continue with the ointment. It was interesting to note that in the subsequent 3 weeks both sides improved equally on the lotion therapy.

Especially noteworthy was the finding that there was a progressive improvement on continued use of the tar-allantoin lotion. Thus, after six weeks, significant improvement was obtained in a total of twenty-five cases, of which six experienced complete clearing.

For purposes of evaluation, the one-plus reactions, indicating mere removal of scales and, of course, the negative results, are considered as therapeutic failures since scale removal is often achieved by application of petroleum jelly alone, and this result could be attributed to the vehicles of the preparation used in the study.

An additional feature that appears worthy of further investigation is our impression that the lotion potentiates such supplementary measures as grenz-ray therapy. Experience has demonstrated that there is no reason to fear using this irradiation concurrently with the lotion.

It should be stressed that the thirty-nine patients in this series have suffered from psoriasis for varying periods of time. Many of these patients had undergone extensive treatment prior to the current study.

TABLE 2
SUMMARY OF RESULTS OF TAR-ALLANTOIN THERAPY

Response	No. of cases
Completely cleared	6
Greatly improved	19
Improvement in scaling alone	3
No improvement	11

It was interesting to note, therefore, that there was no apparent correlation between the duration or type of psoriasis and the results obtained with the tar-allantoin lotion. In any event, the results indicate that more than 50 per cent of our subjects obtained complete clearing to marked improvement in lesions treated with the lotion, as compared with about 18 per cent for lesions with the standard ointment (TABLE 2).

Discussion

It is always desirable, when considering the use of a therapeutic agent, to be in a position to refer to its mechanism of action. We are only now gaining the knowledge of the chemistry and physiology of the skin that will

enable us to attack its disorders, and perhaps to explain why ailments that are more than skin-deep respond to topical medication as often as they do.

Allantoin, according to the literature of two and more decades ago, facilitates removal of necrotic or nonviable tissue, and stimulates healing by promoting cell proliferation. We now learn that allantoin also has a keratin-dispersing action. These properties commend its use in psoriasis especially, since it is stable and well tolerated. I approached the use of the allantoin-tar combination with the same skepticism that I should feel on approaching any new treatment for psoriasis. I was pleased to find that clinical results indicate that this new preparation represents an advance over presently available therapy for psoriasis. The fact that clearing is progressive and continues with prolonged therapy in so many instances is a matter of special interest.

The lotion was well accepted by the patients, who commented that they did not mind using it and that it did not stain their bed sheets or clothing.

No systemic or local sensitivity was encountered.

It is perhaps unnecessary to note, in conclusion, that improvement achieved with the lotion, as with any therapy for psoriasis, can be forfeited if the patient fails to continue on maintenance therapy, which in our experience was determined in each case by individual tendencies toward recurrence.

Summary

Using a "symmetrical paired comparison" method, a new allantoin-coal-tar lotion was evaluated against a standard ointment in 39 psoriatic patients. The new tar-allantoin combination provided a greater degree of improvement in this group of psoriatic patients than any previously used topical therapy. Six of the patients with previously resistant psoriasis cleared completely and an additional 19 improved. It should also be noted that the tar-allantoin combination is not only compatible with grenz-ray therapy, but apparently there is a potentiation when these two modalities are used together. The new preparation, it was found, possesses a number of highly desirable qualities. It produced a substantially higher rate of significant improvement; it proved to be compatible with grenz-ray therapy, with evidence that it potentiated irradiation; it appeared to produce a progressive clearing action on continued application; and it was well tolerated and cosmetically acceptable.

References

1. Sulzberger, M. B., R. L. Baer, A. Kanof & C. Lowenberg. 1946. Methods for rapid evaluation of beneficial and harmful effects of agents applied to the human skin. J. Invest. Dermatol. **7**: 227.
2. Clyman, S. G. 1957. Comparative effects of hydrocortisone and hydrocortisone-coal tar extract creams of atopic dermatitis. Postgrad. Med. **21**: 309.

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